Edited by Tsvetin Genadiev

# Prostatectomy

Chapter 1

# Introductory Chapter: Prostatectomy - Challenge in the Past and Today

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## 1. Prostate and prostate surgery through the centuries

This short historical review shows the meaning of the prostate and the main points in the development of prostatectomy techniques through the centuries. The historical documents reveal the contribution of a large number of names of distinguished doctors and scholars from the ancient centuries to the present day. It is difficult to present this contribution in detail within an article, but it is possible to identify the main points of prostate surgery and their significance these days.

Documents show that the term "prostate" has an ancient origin. The term has been described by ancient anatomists but has become important for urine retention around the middle of the sixteenth century. A century later, metal catheters and tools for urinating through the prostate began to be used.

At the end of the seventeenth and the beginning of the eighteenth century, the urinary stone surgery marked a turbulent development through perineal access to the urethra and bladder. After the profound anatomical studies of the peritoneum by the Douglas brothers, it is clear that the peritoneum can be preserved and separated from the bladder during surgery. John Douglas performed a suprapubic surgery for bladder stones, which he calls as high operation. It replaces the perineal surgery for a short time. This finding can be considered the basis of suprapubic urological surgery. These two surgical techniques—perineal and suprapubic—become the basis of modern prostate surgery.

The introduction of anaesthesia and aseptic treatment began the violent development in urological surgery in the second half and the end of the nineteenth century. A number of remarkable surgeons perform for the first time operations to remove bladder stones and prostate parts through suprapubic access. A new problem faces them—the bladder healing that remains open

after surgery. Surgical progress achieves surgery with primary bladder closure. The enucleation of the whole prostate gland through the operator's finger becomes a key point in this surgery. It has been used to treat enlarged prostate and urine retention. Operative techniques become a challenge for surgeons. Conflicts between remarkable surgeons for pioneering in surgical techniques arise. At that time, these operations were performed to treat urinary retention of the enlarged prostate, and the cancer had not yet been studied. The first described histological case of prostate cancer dates back to the middle of the nineteenth century. The problem is developing vigorously in the early twentieth century with the development and practice. New challenges are found in prostate surgeons—cancer removal. The urologists had hardly achieved successful surgical technique for adenoma and had to experience the new challenge of radical prostatectomy.

In the first half of the twentieth century, the main goal of prostate surgery remains the low mortality and successfully completed surgery, but achieving these goals does not stop the progression of prostatectomy. In addition to open techniques, through perineal, suprapubic, retropubic, inguinal, transcoccigeal, ischiorectal access, transurethral surgery is also widely used in practice. It also provides a combined operation—suprapubic access with transurethral one for good haemostasis.

The development of early diagnosis of prostate cancer sets new goals for urologists—achieving quality of surgery and quality of life for the patient. The investigation of pelvic anatomy leads to the discovery of a new prostatectomy—a nerve-sparing radical prostatectomy. This discovery becomes the basis of all modern surgical techniques for the treatment of prostate cancer. The refinement and standardisation of open surgery for prostate adenoma and prostate carcinoma seem to satisfy the aspirations of modern twentieth century surgery. At the end of this period, the challenge of laparoscopic technique began in various areas of surgery. This technique sets new targets for surgeons—surgery without harm to the patient—a basic law in surgery.

The love of urology and medical dedication to the patient justify this considerable progress of prostatectomy. Today, the technology revolution, along with classical experience, rewarded the surgeon with the introduction of the robotic operation. It protects the surgeon's health and awaits his full dedication to the patient. Nevertheless, the challenges of prostatectomy do not stop. New and new methods based on laparoscopy and transurethral surgery continue to be performed.

## 2. Brief introduction to the chapters

### 2.1. Section prostate diagnosis

The first chapter of this section presents the novel smart method for prostate diagnosis based on the spectroscopy. The method is expected to diagnose the effect of prostate cancer treatment and to provide accurate and personalised patient monitoring. This will improve the healing tactics of each patient.

The second chapter presents and discusses the different invasive and noninvasive biomarkers for prostate cancer early diagnosis and good therapy selection. The genetic diagnosis for prostate cancer is the near future of this field.

The last chapter presents a new diagnostic method for positron emission scanning the prostate cancer, local or metastatic disease, using scandium. This pharmaceutic has a longer half-life than the gallium and has advantages in this diagnostic method.

### 2.2. Section prostatectomy operative techniques

This section introduces new methods for simple and radical prostatectomy. The authors describe the methods and present their results. It is interesting to see the different key points of some classical urological operative techniques and their new applications.

### 2.3. Section prostatectomy recovery and quality of life

The goal of modern radical prostatectomy is not only to be a healing method for prostate cancer but also to achieve good functional outcomes for the quality of life of the patient. This section presents a very extensive and in-depth scientific work on the topic of patient recovery after radical prostatectomy.

## 3. Conclusion

This book is a modest document of contemporary efforts and challenges in the diagnosis and treatment of a significant area of modern medicine—the prostate. There is hardly any other part of urology that has caused such an endless and meaningful century-old progression comparable to that of the prostate gland surgery.

We hope the reader will find answers to his questions and a spark of new challenges to prostatectomy!

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Chapter 2

# Biomarkers for Diagnosis and Prognosis of Prostate Cancer

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**Abstract**

Since its discovery, elevated prostate-specific antigen (PSA) has been the measurement to indicate possibility of prostate cancer, as well as biochemical recurrence following treatment. Although PSA has led to decrease in prostate cancer–related mortalities, PSA is a nonspecific prostate cancer biomarker reflective of other prostate-related conditions such as benign prostatic hyperplasia (BPH), resulting in a high false-positive rate. This has led to overtreatment of men with clinically insignificant disease. While most prostate cancer patients have slowly progressive disease and should be treated conservatively, roughly 10% of patients will progress to have metastatic disease, of which the majority of prostate cancer deaths can be attributed. Stratifying these patients based on prognosis so that they may benefit from aggressive treatment is critical to their survival. Biomarkers for prostate cancer diagnosis and subsequent prognostic screening have significantly advanced this field. Here, we review some of the current blood, tissue, and urine biomarker tools used to measure an array of molecules including DNA, RNA, protein, or even epigenetic modifications. Utilizing the technologies described here, as well as looking to the future, correct early identification of prostate cancer with powerful prognostic value is much closer than ever before.

**Keywords:** prostate cancer, biomarker, early detection, prognosis, risk stratification

## 1. Introduction

Prostate cancer remains the most commonly diagnosed cancer in men in the United States with over 200,000 new cases detected annually [1]. Gleason grade of prostate cancer, developed by Dr. Donald Gleason in the 1960s, remains the most prognostic indicator of prostate cancer to date. Gleason grade ranges from 1 (normal) to 5 (most abnormal) and is assigned based on the histology of prostate tissues from biopsies. The Gleason score ranges from 2

to 10 and is the sum of the two most common Gleason grades. However, assessing Gleason grade requires invasive tissue biopsies. Less than one-third of men tested for prostate cancer through biopsy are diagnosed with cancer by histological analysis. Meanwhile a negative biopsy does little to reassure patients and clinicians of negative cancer status. This leads to a large number of patients undergoing painful initial biopsy procedures that may ultimately be repeated due to uncertainty of diagnosis [2]. Prostate cancer biopsies are a painful and invasive procedure, with the chance of complications including bleeding and infection [3–5].

Of those patients with positive diagnoses, roughly 10% will progress to metastatic prostate cancer, resulting in about 30,000 deaths annually in the United States. It is obvious that these patients should receive aggressive treatment at the earliest sign of disease. However there is concern as to over-diagnosis and over-treatment of indolent prostate cancer [6], resulting in some cases of high risk prostate cancer being treated conservatively with active surveillance, or first step intervention with radiation or radical prostatectomy. It is imperative to the respective disparate patient populations to receive the most accurate, timely, prognostic diagnosis.

The national cancer institute (NCI) dictionary of cancer terms defines biomarker as a "biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or a condition or disease." Advancements in the field of biomarker discovery have shaped the way medicine is performed and patients are diagnosed [7]. Biomarkers are used throughout the scope of clinical progression from early detection and diagnosis through clinical endpoint determinations.

Ideal biomarkers should have high sensitivity and specificity. That is, the power to correctly identify a high proportion of true cases, or those that will experience an event - in this case, developing prostate cancer. A biomarker should also have high specificity, correctly identifying patients who are truly negative for harboring prostate cancer. Typically, a balance is met between specificity and sensitivity. These results are presented as receiver operating characteristic (ROC) curves which are a visual means to describe the statistical ability of a model to correctly classify cases from non-cases [8]. Complete random distribution creates an "area under the curve" or AUC value of 0.50, graphed as a straight slope line, while the value from a perfect prediction model would be 1.0. A reliable prediction model therefore should have an AUC value nearing 1.0.

Here we will discuss the scope of biomarkers currently used for prostate cancer diagnosis, as well as prognosis to aid in disease monitoring and treatment oriented decision-making. Prostate cancer biomarkers are currently among three categories: blood, tissue or urine based biomarkers.

## 2. Blood-based biomarkers

An ideal biomarker screen is non-invasive. Blood collection is considered a minimally invasive technique with quick turnaround time that is also indicative of real-time alterations and disease states in the body, while robust or stable enough for findings to be reproducible across clinics. For prostate cancer as with many other diseases, the use of blood to monitor disease progression was the first and hallmark analysis performed to detect the disease.

In recent years, the phrase "liquid biopsy" has been coined, expanding a simple blood draw into an extensive cancer screen, testing for circulating tumor cells or circulating tumor free DNA in the blood. These tests have shown great promise in detecting cancer at early stages across a wide array of malignancies including prostate cancer [9].

Today, we continue to use blood based screens as means to detect prostate cancer, inform patients and clinicians on necessity of treatment, as well as to plan and monitor treatment response.

### 2.1. Prostate-specific antigen

The discovery of prostate and prostatic fluid associated antigens, most notably prostate-specific antigen (PSA) occurred in 1970 by Richard Ablin [10]. PSA is a glycoprotein produced by human kallikrein-3 (hK3), a member of a class of highly homologous serine proteases, the tissue kallikreins. PSA is normally produced by the epithelial cells of the prostate gland and secreted into the lumen to aid in liquefaction of semen ejaculate. However, other pathological conditions in the prostate, such as benign prostatic hyperplasia (BPH) or prostatitis can elevate the serum PSA levels, resulting in a "false positive" PSA test. PSA concentration in blood has been heavily explored for detection of prostate cancer, as well as treatment response and progression free survival monitoring thereof.

The number of diagnosed prostate cancer cases surged with the implementation of PSA screening tests, peaking at around the time of its approval by the United Stated Food and Drug Administration (FDA) in 1994 for prostate cancer detection. While PSA is prostate specific, it is not, however, specific to cancer, being additionally increased in the aforementioned benign prostate conditions. Since its discovery, PSA has been extensively studied in randomized clinical trials as a screening test for prostate cancer. Despite this discovery, prostate cancer remains the most commonly diagnosed non-cutaneous cancer in men in the United States, with solid tumor-associated deaths only second to lung cancer [1]. In addition to poor cancer specificity, PSA also has low sensitivity. Reported in the prostate cancer prevention trial (PCPT) 15% of men with PSA 0–4 ng/ml have prostate cancer, 15% of those are high Gleason score [11, 12].

Ultimately, implementation of PSA as a screening tool led to an over-diagnosis and subsequent over-treatment of low-risk disease. Perspective studies indicated up to 10% of patients who received curative therapy by either radical prostatectomy or radiation were over-treated [13]. In 2012 The United States Preventative Services Task Force (USPSTF) recommended against PSA based screening for prostate cancer [14]. This recommendation has recently been amended to suggest PSA may be used specifically in men 55–69 on a case-by-case basis with informed patient consent regarding potential harms of screening. In all, the usefulness of PSA will continue to persist especially in disease monitoring, but recent advances lose faith in PSA alone as a diagnostic tool. In-depth analysis of PSA has revealed several molecular variations and functions of PSA which may prove to be more specific to cancerous tissues.

#### *2.1.1. Free vs. bound PSA*

PSA is typically observed complexed to protease inhibitors such as alpha 1-antichymotrypsin (ACT) or alpha 2-macroglobulin, known as bound PSA [15, 16]. Discovered in the 1990s, a

higher ratio of free PSA, that is, not bound to protease inhibitors and considered inactive, is associated with increased likelihood of BPH rather than cancer [15, 17–19]. Specific assays have also been developed to measure bound PSA (complexed-PSA), which is usually PSA-ACT and is elevated in cancer [20]. A percentage free PSA (free PSA/total PSA) can be calculated, and is typically lower in men with prostate cancer [21], where early studies linked <25% free PSA to detection of prostate cancer with a sensitivity of 95% [22]. However, follow-up analyses have had less promising results likely due to the relative instability of free or uncomplexed PSA compared to bound, making this an unreliable clinical parameter for patient diagnosis [23, 24].

#### *2.1.2. Proenzyme PSA (proPSA)*

Free PSA can be found in three different forms; proenzyme PSA (proPSA), benign PSA (BPSA) and intact PSA. proPSA is found increased in patients with prostate cancer [25, 26]. Several isoforms exist of proPSA based on varying truncations including [−2] and [−4] proPSA. [−2] proPSA or p2PSA has shown promise as a prostate cancer biomarker as it is not detected in BPH, and in trials increased the AUC from 0.52 for PSA or 0.53 for percentage free PSA to 0.73 [27]. [−2] proPSA has been used preferentially to total or free PSA for prostate cancer detection or biopsy [28–30].

#### *2.1.3. Prostate-specific antigen density (PSAD) test*

The PSAD test attempts to add specificity to PSA testing in prostate cancer by determining the amount of PSA produced in relation to size of the gland, as size has been highly correlated with prostate cancer prognosis [31, 32]. Prostate size can be measured with magnetic resonance imaging or transrectal ultrasound by a physician. High density indicates that a small volume prostate is responsible for making a large amount of PSA, and reflective of prostate cancer. In contrast, low density reflects an enlarged prostate, most likely due to BPH that is responsible for the PSA elevation.

#### *2.1.4. PSA velocity*

Another factor suggested to provide more accuracy to PSA in ability to predict prostate cancer lies in the rate at which increase is observed, referred to as PSA velocity. PSA testing is performed at routine intervals in men on active surveillance, and elderly men at risk of developing prostate cancer. Elevated PSA is considered in the range of 4.0–10.0 ng/ml, though prostate cancer may still be found in men below this range. PSA velocity factors the rate of PSA increase over time, such that an increase greater than 0.5 ng/ml per year may be indicative of prostate cancer [33].

### 2.2. The prostate health index

The Prostate Health Index (PHI) is an intuitive formula based upon utilization of several well characterized PSA forms—total PSA, free PSA, and [−2] proPSA or p2PSA, such that:

$$\left(\frac{p2PSA}{free\ PSA}\right) \times \sqrt{PSA} \tag{1}$$

The PHI's multifactorial approach has compounded the precision of each of the PSA measurements providing one patient score, shown to drastically increase the specificity for prostate cancer [28, 34]. PHI has been approved by the FDA for men with PSA in the 4.0–10.0 ng/ml range.

Several clinical trials have retrospectively performed direct comparison to PHI against other early detection biomarkers across blood or urine analysis. In a European cohort of men undergoing either an initial or repeat biopsy, comparing PHI to PSA or free PSA, PHI increased the AUC values to 0.70 compared to 0.65 or 0.53 respectively [35]. In one prospectively performed trial it was determined that 30.1% of patients who underwent a biopsy could have been spared the painful procedure based on PHI score [36]. PHI has additionally been compared against urine biomarkers (to be discussed further in this chapter), with PHI increasing AUC over PCA3 or TMPRSS2:ERG [35, 37]. While results were similar, PHI was the only one correlated with Gleason grade greater than 7 [38].

### 2.3. The four-Kallikrein panel and 4Kscore® test

The four-kallikrein panel, subsequently referred to as the 4Kscore test is a reflex, or follow-up blood test for men who have an abnormal PSA or digital rectal exam (DRE) result and are being considered for an initial or repeat prostate biopsy after a prior negative biopsy result. True to its name, the test is based upon inclusion of four–kallikreins, total PSA, intact PSA, free PSA in addition to human kallikrein-2 (hK2). The test is generated by OPKO Labs (Nashville, TN) and has been marketed as accurately identifying the risk of aggressive prostate cancer (Gleason >7) in a subsequent biopsy or radical prostatectomy, aiding in patient action plan–based decision making.

The first clinical report of the four-kallikrein panel was among 740 previously unscreened men who underwent biopsy for a PSA above 3.0 ng/ml in the European Randomized Study of Screening for Prostate Cancer [39]. Subsequent studies have been performed for at least 10 cohorts totaling over 15,000 subjects (reviewed in [40]), each of which observed an AUC between 0.80 and 0.90 for the four-kallikrein testing. Results from these studies consistently demonstrate the four-kallikrein panel effectively identified high-grade disease while reducing the number of unnecessary biopsies 49–57% among men being screened for the first time. The 4 k panel is the only test, aside from PSA that has been linked to long-term end-points including prostate cancer metastasis [17, 41]. Studies were initially performed in Europe, and limitations include only retrospective analysis, in primarily white populations with an alternative Gleason scale used. In translation to the United States to incorporate FDA guidelines, modifications of the test were implemented with positive results.

### 2.4. Stockholm-3

The Stockholm 3 model (S3M) is a combination of blood biomarkers initially including PSA, free PSA, intact PSA, hK2, MSMB, MIC1, genetic polymorphisms (SNPs) and other variabilities such as age, family history, previous prostate biopsies or exam [42, 43]. Later algorithm modification replaced intact PSA with HOXB13 [44]. The goal of the study was to increase the accuracy of high-risk prostate cancer diagnosis. S3M was tested in over 100,000 men, 50–69 years of age with no diagnosis of prostate cancer in Stockholm, Sweden [42, 43]. The performance

of S3M was compared to PSA alone. The use of S3M was found to decrease the number of biopsies by more than 50%, avoid negative biopsies and significantly improve the detection of high-risk prostate cancer [42, 43].

### 2.5. Prostate-specific membrane antigen

Prostate-specific membrane antigen (PSMA) is another glycoprotein with enzymatic function uniquely expressed in the prostate. As its name suggests, what makes it unique from PSA is that it is not a secreted protein, rather it is an integral membrane protein. Yet, like PSA, PSMA is also not specific to prostate cancer.

While PSMA has had little success as a serum based diagnostic marker, it is now being used as the target of an FDA approved radiographic scan (ProstaScint) in which an antibody against PSMA (7E11) is linked to a radiographic agent $^{111}$indium. ProstaScint increased predictive value for metastatic prostate cancer, identifying positive lymph node metastases [45]. Several new PSMA specific tracers have been developed for use in PET and PET/CT scanning with performance characteristics that exceed those of ProstaScint and are likely to be approved soon for clinical use.

### 2.6. Prostatic acid phosphatase

Prostatic acid phosphatase (PAP), or prostatic specific acid phosphatase (PSAP) is a glycoprotein enzyme secreted by prostate cells like PSA. Discovered in the 1930s as a diagnostic biomarker [46], it was replaced with the discovery of PSA in the 1970s. However, PAP reemerged following the discovery that PAP was highly expressed in correlation with tumor staging, and is the target of the first prostate cancer immunotherapy, Sipuleucel-T, approved by the FDA in April, 2010 [47, 48], and which increased overall survival of men with metastatic prostate cancer in its first IMPACT trial [49].

### 2.7. AR-V7

Androgen receptor splice variant 7 (AR-V7) is a splice variant of androgen receptor (AR) that lacks the ligand binding domain leading to its constitutive transcriptional activity independent of androgens. Due to its androgen independent function, AR-V7 has been implicated in the resistance to second-generation anti-androgen therapies. AR-V7 can be detected in circulating tumor cells (CTCs) and its presence is correlated with resistance to second generation anti-androgens including enzalutamide and abiraterone [50, 51]. These results suggest the use of AR-V7 as a treatment selection biomarker.

## 3. Tissue-based biomarkers

Tissue based prognosticators are among the most diverse in functionality. Tissue based assays can be performed from as little tissue as a single core of a biopsy up to radical prostatectomy. Yet, these assays are the most invasive due to the nature of tissue extraction through surgical resection or biopsy. Patients may undergo one or multiple sets of biopsies in the course of disease detection and active surveillance. Biomarker screening may also be performed on

patients post radical prostatectomy to predict treatment response, recurrence free survival and likelihood of disease progression. Many of these tests are commercial panels available to analyze multiple mRNA signatures in the prostate, but recent advancements in protein and cancer epigenetics are expanding the possibilities of prostate cancer prognosis. Assays are monitored by The National Comprehensive Cancer Network (NCCN), an alliance of U.S. cancer centers directing clinical practice guidelines, as well as the Food and Drug Administration (FDA).

Here we will discuss several of the most commonly used tests:

### 3.1. DNA

Deoxyribonucleic acid (DNA) is the genetic material of all living things. In comparison to other cancers, prostate cancer has little in the way of genetic mutations. Researchers have used the several well described genomic alterations to their advantage as prognosticators of disease.

#### *3.1.1. Epigenetic testing*

Current biopsy strategies sample areas of the prostate in a gridded fashion in attempt to have the most representative assessment of the prostate. Even with this strategy in place, less than 1% of the prostate is sampled. As less than one-third of biopsies return positive results for cancer, there is large concern over inconclusive biopsy results.

The field cancerization effect was first observed in the 1950s when it was noticed that tissues surrounding cancerous lesions contained markers associated with tumor development of oral squamous-cell carcinoma [52]. This phenomenon has since been observed in most solid tumors. Further understanding of the concept is explained in [53]. Today, field effect can translate to modifications in cellular morphology, epigenetics, genomic or mitochondrial DNA alterations, and changes in gene expression or protein levels (reviewed in [54]).

One such assay, ConfirmMDx, tests the epigenetic field effect by observing the molecular changes in methylations occurring in prostate cancer. DNA methylation is among the most common measures of epigenetic abnormality, and easiest to test. These alterations are not detectable in histological analyses, but visible with methylation specific PCR (MSP). Biologically these methylations may be responsible for silencing of key tumor-suppressive genes critical to preventing cancer development, and because of the cancer field effect, this test dramatically amplifies the tested area of the prostate. ConfirmMDx is recommended for men having undergone an initial negative biopsy.

Prostate cancer-associated epigenetic biomarkers used in this assay include glutathione S-transferase-Pi (GSTP1), APC and RASSF1. Methylation of GSTP1 is among the most common somatic alterations observed in prostate cancer with high specificity and sensitivity, and which correlates strongly with Gleason score, age, PSA and DRE [55–57].

#### *3.1.2. PTEN loss and ERG rearrangements*

Phosphatase and tensin homolog (PTEN) is a tumor suppressor commonly lost in many cancers. Loss of PTEN is one of few genomic alterations occurring in prostate cancer. PTEN deletion associates with poor outcome and is an established prognostic biomarker for prostate

cancer. Analysis of prostatic tissue by Immunohistochemistry (IHC) or Fluorescence in situ hybridization (FISH) demonstrated that PTEN loss is associated with prostate cancer biochemical recurrence, disease progression and metastasis [58–63].

TMPRSS2:ERG fusion is found in ~50% of prostate cancer [64, 65]. TMPRSS2:ERG is a result of gene rearrangement and fusion between androgen regulated transmembrane protease, serine 2 (TMPRSS2) and ERG transcriptional factor genes [64, 65]. This leads to significant overexpression of ERG reported to promote prostate cancer oncogenesis [66–70]. TMPRSS2-ERG rearrangements are accompanied by PTEN loss, which cooperates to promote prostate cancer progression [69, 70]. Moreover, loss of PTEN and presence of TMPRSS2:ERG fusion together predict prostate cancer biochemical recurrence [71] and Metamark further provides screening for loss of PTEN and ERG rearrangement in their PTEN/ERG screen.

### 3.2. mRNA

Messenger RNA or ribonucleic acid (mRNA) is genetic material carrying information between DNA and protein.

#### *3.2.1. The genomic prostate score*

Oncotype DX offers a diverse array of genomic health testing including breast, colon and prostate cancer. The Genomic Prostate Score (GPS) is a prostate specific array which aids in decision-making between initiating immediate treatment or active surveillance. The test measures expression from 12 genes in four prostate cancer associated biological pathways: androgen signaling (AZGP1, FAM13C, KLK2, SRD5A2), cellular organization (FLNC, GSN, GSTM2, TPM2), stromal response (BGN, COL1A1, SFRP4) and cellular proliferation (TPX2), as well as 5 reference genes (ARF1, ATF5E, CLTC, GPS1, PGK1) [72]. This assay has been validated prospectively as an independent predictor of tumor aggressiveness based on adverse pathology, and death associated with prostate cancer and metastasis [73, 74]. GPS is advised for patients with low-risk clinical prostate cancer (very low, low or intermediate NCCN risk). AZGP1 was further validated as a potential biomarker for significant disease [75]. Loss of AZGP1 assessed by RNA in situ hybridization and immunohistochemical analysis is associated with worse outcome and overall survival [75].

#### *3.2.2. Prolaris*

Prolaris is a prognostic genetic test developed by Myria Genetic Laboratories based on a 46-gene expression signature strongly tied to cell cycle progression genes. Uniquely paired with cellular proliferation and Gleason grading, The Prolaris Score is generated as a metric of an individual's prostate cancer aggressiveness. This score provides a relative risk among patients of the same risk group defined by the American Urological Association (AUA), and a 10-year prostate cancer specific mortality risk in men with localized disease [76].

#### *3.2.3. Decipher*

The Decipher Biopsy was generated from GenomeDX, based on whole genome technology. In men with localized prostate cancer undergoing biopsy or radical prostatectomy, this test divides patients into Low Risk or High Risk, aiding clinicians and patients in decision making

toward active surveillance or intensification of treatment with multi-modal therapies. Decipher Biopsy measures 22 RNA biomarkers to correlate the probability of clinical metastasis within 5 years following radical prostatectomy [77] and is predictive of lymph node metastasis [78]. This test can be performed on either biopsy or prostatectomy samples reproducibly [79].

### 3.3. Protein

#### *3.3.1. ProMark*

ProMark is the first protein based prognostic test for prostate cancer from Metamark Genetics Inc. Based on the understanding that mRNA levels may not be completely reflective of a diseased state, ProMark assays protein levels in intact, formalin fixed biopsy samples to infer prognostic information about the patients' condition at the time of biopsy. Based on a quantitative multiplex immunofluorescence (QMPI) platform in which tissues are fixed in formalin, samples are stained for eight protein markers for cancer and normal regions and quantified in situ [80]. Markers include SMAD4, PDSS2, HSPA9, FIS, pS6, and YBOX1 to designate regions of prostate cancer, as well as proteins found in tumor and benign tissues, DERL1 and CUL2. Selected by computational modeling, these combinations of protein markers reflect the morphology from tumor epithelium for reliable prognostication [80–82]. Cost to perform ProMark protein screening is additionally quite low compared to usual guideline-based care [83]. ProMark has been utilized in clinical studies to predict lethal outcome. The test is currently recommended for men with Gleason grade 3 + 3 or 3 + 4 prostate cancer as part of the NCCN Clinical Care Guidelines.

#### *3.3.2. p63 and AMACR*

p63 has been identified as a marker of basal cells in multiple epithelial tissues including normal prostate [84]. Significant downregulation or loss p63 is commonly observed in prostate cancer [84, 85]. Alpha-methylacyl coenzyme A racemase (AMACR) is commonly found overexpressed in prostate cancer and exhibits little to no expression in the normal prostate tissues [86–89]. A combination of high-molecular weight cytokeratins, AMACR and loss of p63 can be used to define normal prostate tissues, prostate intraepithelial neoplasia and prostate adenocarcinoma [90, 91].

## 4. Urine biomarkers

Urine analysis is a non-invasive screening technique for prostate cancer.

### 4.1. PCA3

Prostate cancer antigen 3 (PCA3) (also known as DD3) is a non-coding mRNA specifically expressed in human prostate tissues, and highly overexpressed in prostate cancer [92].

The Progensa PCA3 assay is an FDA approved urine based molecular test to aid in repeat biopsy decisions from Hologic [93]. Following DRE, a simple "first-catch" urine test captures prostate epithelial cells released into the urine. PCA3 mRNA levels are quantified in proportion to PSA. Also included in the NCCN's Clinical Practice guidelines for prostate cancer early

detection, this test's specificity lies in PCA3 which is highly upregulated in prostate cancer cells and not affected by instances of benign prostatic hyperplasia (BPH), prostatitis or other conditions as is the case for PSA. PCA3 testing is currently FDA approved for men previously having a negative biopsy with a persistently elevated PSA to help identify men who need a repeat biopsy. PCA3 is calibrated to identify men at low risk for a positive biopsy such that PCA3 < 25 indicates that it is safe to forgo the biopsy. Increase in score was directly correlated with likelihood of positive repeat biopsies, and predictive of 4-year biopsy outcome [94–96]. PCA3 has subsequently been explored and proven to positively predict detection of prostate cancer in initial biopsies with high specificity and may aid in initial biopsy decision making [97, 98].

### 4.2. SelectMDX

Utilizing first catch post-DRE urine, SelectMDx tests for mRNA levels of genes DLX1 and HOXC6. Analysis for this test incorporates multifactorial data from PSA density and prior biopsy data to increase significance of this liquid biopsy. This test has shown promise over PCA3 in two prospective clinical trials in identification of patients with high-grade prostate cancer (AUC of 0.90 in first cohort and 0.86 in validation cohort) [99]. SelectMDx was recently added to the European Association of Urology's list for added decision making before a repeat biopsy.

### 4.3. TMPRSS2:ERG

As ERG rearrangements occur at the genomic level, prostate cancer associated gene fusions such as TMPRSS2:ERG rearrangements are also detectable in patient urine [71, 86–89]. Urine TMPRSS2:ERG was found to associate with Gleason score and tumor size in a large multicenter study with 1312 men [100]. This strategy utilizes transcription mediated amplification (TMA) assay to quantify TMPRSS2-ERG mRNA normalized to PSA mRNA. Additionally, it was demonstrated that the combination of urine TMPRSS2:ERG with urine PCA3, improves the performance of serum PSA for predicting prostate cancer risk [100–102].

### 4.4. Mi-prostate score (MiPS)

The Michigan Prostate Score (MiPS) combines serum PSA levels with urine analysis for TMPRSS2:ERG and PCA3 mRNA as a predictive model for a positive prostate cancer biopsy. This compounded analysis of three independent prostate markers are closely correlated with presence of prostate cancer in an initial or repeat biopsy and provides a more accurate predictive model of biopsy detected prostate cancer [101].

### 4.5. Extracellular vesicles

Exosomes are small extracellular vesicles secreted from cells ranging in size from 30 to 120 nm. A portion of the parent cell cytoplasm is contained inside each exosome for the biological function of cell-to-cell communication. For the purpose of clinical diagnostics, this mechanism can be manipulated to measure exosomal genetic material released into blood, urine or other biological fluids. RNA expression from tumor cells is promising as they are highly representative of cell of origin. As exosomes are secreted freely into the urine, exosomal based testing does

not require biopsies to detect oncogenic signatures [103, 104]. For instance, PCA3 and ERG mRNAs can be detected in exosomes and be predictive for high grade prostate cancer [105].

### 4.6. ExoDX prostate (IntelliScore)

Exosomal analysis of PCA3 and ERG RNA copy number from prostate cancer patient urine was determined to positively predict presence of high-grade prostate cancer [105, 106]. This test, now marketed as ExoDX *Prostate(IntelliScore)* is considered a liquid biopsy, combining urine with PSA screening from blood sample. Clinically, *Prostate(IntelliScore)* correctly predicts the occurrence of Gleason scores above 7, and has been recommended for men over 50 with PSA levels in the 2–10 ng/ml range. Further evaluation of this biomarker assay is currently underway.

New technologies are expanding to increase the capture and analysis for extracellular vesicles as experimental material. Exosome Diagnostics, who market the ***Prostate(IntelliScore)*** additionally provide isolation kids for exosomal RNA. Alternatively, devices such as the Exosome Total Isolation Chip (ExoTIC), have been generated specific for the high-yield isolation of extracellular vesicles from biofluids (blood, urine, and lavage), even allowing for separation among vesicles based on size. This work has initially been applied to protein and microRNA analysis, increasing the scope of assayable markers for prostate cancer [107].

## 5. Conclusions

Assays and technologies have vastly improved prediction strategies for recurrent prostate cancer and metastatic disease. Collectively, the biomarkers and assays presented within this chapter represent great advances in the diagnosis and prognostic assessment of patients with prostate cancer and aid in decision-making for subsequent treatment strategies (reviewed in **Table 1**). However, even with this extensive armamentarium there is still improvement to be made in risk-stratification to accurately identify patients with cancer, and among them, those at risk of developing high grade disease. As biomarkers become available it is increasingly important to understand how these tests are helpful to know when and on which patients these tests should be utilized. Guidelines for care are consistently monitored by urological associations globally. While recommendations vary based on country and among individual institutions and providers, more than ever, patient led decision making is at the forefront of screening. This was evidenced by USPSTF's recent removal of PSA screening for healthy men as routine procedure, instead recommending individualized decision-making by physician counseling of patients as to the potential risks of inaccurate diagnosis leading to over-treatment.

Human nature understandably dictates a need for testing to be as minimally invasive as possible to eliminate painful procedures, and increase patient compliance and willingness to participate in early disease screening. The development of non-invasive screening methods such as blood and urine assays to limit prostate biopsy aids in reducing painful, and in the case of prostate cancer, often unnecessary procedures. This is even further amplified when taken into account the number of men who have to undergo the biopsy procedure repeatedly in the course of diagnosis and disease progression. The future of cancer screening, and hopefully diagnosis will come

| Test | Specimen | Invasive | Implication | Biomarkers tested | Genetic Material Tested | FDA Status | Sources |
|---|---|---|---|---|---|---|---|
| PSA | Blood | Non-invasive | Treatment response and progression free survival | PSA | Protein | Approved | [10-33] |
| Prostate Health Index (PHI) | Blood | Non-invasive | Risk-assessment and repeat biopsy decision | total PSA, free PSA, [-2]proPSA | Protein | Approved | [28,34-38] |
| 4Kscore | Blood | Non-invasive | Risk-assessment | total PSA, intact PSA, free PSA, hK2 | Protein | total PSA, free PSA- Approved; 4kscore- CLIA | [17,39-41] |
| Stockholm-3 | Blood | Non-invasive | Risk-assessment | PSA, free PSA, hK2, MSMB, MIC1, HOXB13, clinical variables, genetic markers and prostate examination | Protein/DNA | None | [42-44] |
| AR-V7 | Blood | Non-invasive | Therapy resistance | AR-V7 | RNA | CLIA | [50,51] |
| ConfirmMDx | Tissue | Invasive | Risk-assessment and repeat biopsy decision | Methylated GSTP1, APC and RASSF1 | DNA | CLIA | [55-57] |
| PTEN/TMPRSS2:ERG | Tissue | Invasive | Risk-assessment and treatment planning | PTEN and ERG | DNA | CLIA | [58-71] |
| Oncotype DX Genomic Prostate Score | Tissue | Invasive | Risk-assessment and treatment planning | AZGP1, FAM13C, KLK2, SRD5A2, FLNC, GSN, GSTM2, TPM2, BGN, COL1A1, SFRP4, TPX2 | RNA | CLIA | [72-75] |
| Prolaris | Tissue | Invasive | Risk-assessment and treatment planning | 46 RNA biomarkers, Gleason score | RNA | CLIA | [76] |
| Decipher | Tissue | Invasive | Treatment planning | 22 RNA biomarkers | RNA | CLIA | [77-79] |
| ProMark | Tissue | Invasive | Risk-assessment and treatment planning | SMAD4, PDSS2, HSPA9, FUS, pS6, YBOX1, DERL1, CUL2 | Protein | CLIA | [80-84] |
| Progensa | DRE Urine/Blood | Non-invasive | Risk-assessment and repeat biopsy decision | PCA3 and PSA | RNA/Protein | Approved | [92-98] |
| SelectMDx | DRE Urine/Blood | Non-invasive | Repeat biopsy decision | DLX1, HOXC6 and PSA | RNA/Protein | Exempt | [99] |
| TMPRSS2:ERG | Urine | Non-invasive | Risk-assessment | TMPRSS2:ERG | RNA | CLIA | [71][86-89][100-102] |
| MiPS | Urine/Blood | Non-invasive | Risk-assessment | TMPRSS2:ERG, PCA3, PSA | RNA/Protein | CLIA | [101] |
| ExoDX Prostate (Intelliscore) | Urine/Blood | Non-invasive | Risk-assessment, active surveillance monitoring | ERG, PCA3, PSA | Exosomal RNA | Exempt | [105-107] |

**Table 1.** Screening assays for prostate cancer, classified by specimen and genetic material tested, invasiveness of the assay, clinical uses, biomarkers tested, and status of FDA approval. Certain tests have been proven exempt from FDA regulations, and these are also specified. The Clinical Laboratory Improvement Amendments (CLIA) certifies clinical laboratory developed tests to perform additional testing.

from less invasive procedures. One such advance may be the implementation of imaging strategies such as multi-parametric magnetic resonance imaging (mpMRI) to locate and diagnose prostate cancer. Offered prior to biopsy, patients with negative results are spared the biopsy, while those with cancerous lesions can undergo a targeted biopsy aided by mpMRI, minimizing

complications, and obtaining accurate biopsies with ample cancer tissue to aid in treatment plan determination. This technique has tested more accurate than standard of care transrectal ultrasound (TRUS) biopsy in predicting presence of aggressive prostate cancer [108]. The role of imaging in prostate cancer diagnosis is still evolving and these technologies stand to introduce new avenues to the field of prostate cancer diagnosis and even treatment which may lead to better patient risk-stratification with increased survival rates of aggressive prostate cancer.

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## Conflict of interest

The authors declare no conflicts.

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Chapter 3

# Pre-Therapeutic Dosimetry Employing Scandium-44 for Radiolabeling PSMA-617

Elisabeth Eppard

**Abstract**

In recent years, the positron emitter scandium-44 moved into the focus of research providing favorable nuclide properties for an application in nuclear medicine. Radiolabeling of PSMA-617 with scandium-44 as diagnostic match for [$^{177}$Lu]Lu-PSMA-617 instead of gallium-68 would enable pre-therapeutic dosimetry in clinical setting. Due to the chemical similarities of scandium and lutetium, the in vitro and in vivo characteristics of [$^{177}$Lu]Lu-PSMA-617 are more similar to [$^{44}$Sc]Sc-PSMA-617 than to the $^{68}$Ga-compounds [$^{68}$Ga]Ga-PSMA-617 or [$^{68}$Ga]Ga-PSMA-11. [$^{44}$Sc]Sc-PSMA-617 showed its potential in a clinical setting as a PET imaging agent of prostate cancer providing several advantages over gallium-68 labeled tracers. The longer half-life of the nuclide would allow, for example, an optimized patient management and treatment, long-term or late time point imaging as well as transportation to more distant PET centers. However, especially clinical applications like individual dosimetry or intraoperative applications are still under investigation.

**Keywords:** scandium-44, PSMA-617, dosimetry, theranostic, castrate-resistant prostate cancer

## 1. Introduction

Prostate carcinoma is the fourth most common cancer in both sexes combined, the second most common cancer in men, and with an estimated 307,000 deaths in 2012, it is the fifth leading cause of death from cancer in men [1]. While prognosis of prostate carcinoma is good at an early stage, the 5-year survival of patients in advanced stages decreases to 31% [2, 3]. Consequently, a number of studies were conducted developing new strategies against the disease.

As the prostate-specific membrane antigen (PSMA) is overexpressed on prostate carcinoma and the neovasculature of most of the solid tumors but not of normal tissue, it is an attractive target for imaging and therapy [4]. Consequently, the development and the evaluation of small ligands targeting PSMA are the objectives of various studies.

With the introduction of PSMA-617, a further development of PSMA-11, a highly potent theranostic agent found its way into clinical routine where it is used as [$^{68}$Ga]Ga-PSMA-617 for PET and as [$^{177}$Lu]Lu-PSMA-617 for therapy of metastatic castrate-resistant prostate cancer (mCRPC). In the last few years, several studies proved the therapeutic efficacy of [$^{177}$Lu]Lu-PSMA-617 in mCRPC patients [2, 3, 5]. Although [$^{177}$Lu]Lu-PSMA-617 exhibited a favorable safety profile in mCRPC patients [2, 3, 5–9], adverse effects were due to physiologic expression of PSMA in small intestine, proximal renal tubules and salivary glands are observable [2, 10, 11]. Correspondingly, organs at risk are kidneys as well as salivary and lacrimal glands. First experiences showed that pre-therapeutic dosimetry might support pre-selection of patients as well as improvement of individualized therapy planning [7, 9, 12–15]. In this context, pre-therapeutic estimation of dose delivered to PSMA expressing tissue as well as whole body would be useful to predict therapeutic effect of a certain administered therapeutic activity and facilitate individual dose adjustment [16]. For this purpose, [$^{177}$Lu]Lu-PSMA-617 planar ± SPECT imaging, employing small amounts of tracer, or [$^{68}$Ga]Ga-PSMA-617 PET were considered [10–14, 17–19] but both tracers have disadvantages and limitations for dosimetry in a clinical setting.

Current studies on radiolabeling PSMA-617 with the positron emitter scandium-44 demonstrated its similar in vitro and in vivo properties compared with [$^{177}$Lu]Lu-PSMA-617 [20, 21]. As it is combining the similar pharmacokinetics to [$^{177}$Lu]Lu-PSMA-617 with more appropriate nuclide characteristics than [$^{68}$Ga]Ga-PSMA-617, it is assumed to improve pre-therapeutic dosimetry [20, 21].

## 2. Part I: Radiochemistry

Currently, [$^{68}$Ga]Ga-PSMA-11 is the most frequently used PET tracer, targeting the prostate-specific membrane antigen, worldwide [22, 23]. Gallium-68 has for PET imaging appropriate decay properties; nevertheless, its disadvantages limit its application.

Its high positron energy compared to fluorine-18 (cf. **Table 1**) leads to images tending to be noisier while its short physical half-life only covers imaging periods of a few hours. Moreover, the differences in coordination chemistry between gallium-68 and lutetium-177 lead to deviations in pharmacokinetics [20]. As a consequence, gallium-68 is not the nuclide of choice for late time imaging, extended dosimetric evaluations as well as intraoperative applications several hours post-injection (p.i.).

From this point of view, scandium-44 is a genuine alternative to gallium-68 and is in the focus of current research [20, 25–30].

Scandium-44 ($\beta^+$ = 94%, $\tilde{E}_\beta$ = 0.632 MeV) has a physical half-life of 3.97 h and can be produced on two different ways, via $^{44}$Ti/$^{44}$Sc-generator or cyclotron [30–36]. Another potential advantage of scandium(III) in nuclear medicine is its radioisotope scandium-47 ($\beta^-$, primary ◎-ray of

| Positron emitter | Half-life | $\tilde{E}_{\beta}$ | $E_{\beta, max}$ |
|---|---|---|---|
| | | (MeV) | |
| $^{68}$Ga | 67.71 min | 0.829 | 1.899 |
| $^{44}$Sc | 3.97 h | 0.632 | 1.474 |
| $^{15}$O | 2.04 min | 0.735 | 1.732 |
| $^{18}$F | 109.77 min | 0.250 | 0.634 |

**Table 1.** Comparison of mean ($\tilde{E}_{\beta}$) and maximum ($E_{\beta, max}$) positron energies of scandium-44 with gallium-68, fluorine-18 and oxygen-15 [24].

159 keV and t½ = 3.3 d) which is suitable for therapeutical application. Constituting a matched pair of radioisotopes real Sc-labeled theranostic radiopharmaceuticals are applicable [28, 31, 37–40].

Scandium-44 can be quantitatively detected via its 511 keV emission. High radioactivities of scandium-44 can be measured in a dose calibrator applying the $^{18}$F-setting. But due to different radionuclide characteristics, a multiplication factor has to be used, which is depending on the dose calibrator.

Since the 1980s, several radiolabeling studies with scandium radionuclides have been published [20, 21, 25, 28, 38, 41–44]. Chemically, scandium is similar to $Y^{3+}$ and lanthanides. However, the ionic radius of $Sc^{3+}$ is smaller than that of lanthanides for the coordination number 6 while at the same time, it is larger than any trivalent 3d transition metal cation. The most common coordination number of $Sc^{3+}$ is six; nevertheless, examples for coordination numbers between three and nine exist [45, 46].

In vivo stability of a radiopharmaceutical is a crucial factor for clinical application; macrocyclic ligands are the ligands of choice forming thermodynamically and kinetically stable complexes with trivalent hard metal cations. Chemical and, at the end, biological behavior of the complex and consequently of the radiopharmaceutical depend on structural factors, for example, rigidity, cavity size and nature and number of the donor atoms chelating the metal cation [47]. Due to the similarity between $Sc^{3+}$ and $Ga^{3+}$, $Y^{3+}$ or trivalent lanthanides, DOTA, a common ligand in nuclear medicine, was evaluated with regard of its usability [48]. The study revealed that the stability constant of [Sc-DOTA] is comparable with those for $Y^{3+}$ or the heaviest lanthanides and higher than those for $In^{3+}$ and $Ga^{3+}$ as well as the eight-coordination geometry of the complex in solution [48].

Together with its four times longer half-life than gallium-68 and its coordination chemistry similar to lutetium-177, scandium-44 enables longer imaging periods covering up to 24 h post injection as well as improved pre-therapeutic dosimetry.

### 2.1. Production of scandium-44

Scandium-44 can be produced via $^{44}$Ti/$^{44}$Sc-generator [30, 31, 40]. Despite the advantages of the radionuclide generator system prevents the availability of titanium-44 the production

of this generator. Titanium-44 with its half-life of 60 years is only producible with limited yields and at high costs by a small number of facilities [49]. Accordingly, accessibility of the daughter scandium-44 by cyclotron production is an alternative as it provides scandium-44 in sufficiently high yields with radionuclidic purities >99% avoiding the problem of $^{44}$Ti-waste management.

*2.1.1. Cyclotron production*

Growing interest in scandium-44 as alternative to gallium-68 predicated research for production routes providing scandium-44 in the GBq range. Recent intermediate cyclotrons allow an economic production of the radionuclide utilizing p, d or $\alpha$-particle-induced reactions (cf. **Table 2**) [26, 27, 33, 50–57]. The isomer scandium-44m ($T_{1/2}$ = 58 h) has also nuclide characteristics, which can be useful in nuclear medicine [26, 43].

Recently, the accessibility of scandium-44 via proton irradiation of natural calcium targets was described [53] as well as the employment of enriched calcium targets optimizing radionuclidic purity of the radionuclide produced [52].

Similar experiments performed by bombarding natural calcium targets with protons were reported [53, 55], yielding more than 650 MBq scandium-44 with 95.8% radionuclidic purity [53]. As this method leads to co-production of long-living radionuclidic impurities accounting for unnecessary doses for the patient its usability is limited. To obtain scandium-44 of higher radionuclidic purity enriched [$^{44}$Ca]$CaCO_3$ target material was found to be optimal [59]. This study also confirmed an optimal ratio of scandium-44m to scandium-44 by irradiating the targets with 9 MeV protons and the possibility to achieve yields in the GBq range utilizing this method [59]. Further refinement leads to reproducible production of GBq-activities of scandium-44 at a cyclotron in excellent quality [56]. As a result of all these investigations towards scandium-44 production, the basis for the introduction of scandium-44 into clinical routine for PET imaging may have been created.

Nuclide production via cyclotron is in need for an efficient separation strategy of the produced radionuclide from the target material. This is necessary to remove bulk metal, which disturbs eventual radiolabeling of PET tracers, to reduce the volume and to recover target material. For this purpose, different methods such as filtration [53] or ion exchange employing chelating resins were investigated [26, 55, 56, 59].

| | **Reaction** | **Q (MeV)** | **$E_{th}$ (MeV)** |
|---|---|---|---|
| p | $^{44}$Ca(p,n)$^{44}$Sc | −4.43 | 4.53 |
| d | $^{44}$Ca(d,2n)$^{44}$Sc | −6.65 | 6.96 |
| | $^{44}$Ca(d,n)$^{44}$Sc | 0.0 | 0.0 |
| $\alpha$ | $^{44}$Ca($\alpha$,3np)$^{44}$Sc | −32.73 | 35.71 |
| | $^{43}$Ca($\alpha$,2np)$^{44}$Sc | −21.59 | 23.61 |
| | $^{42}$Ca($\alpha$,np)$^{44}$Sc | −13.67 | 14.97 |

**Table 2.** Nuclear reaction data for the formation of scandium-44 [58].

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### *2.1.2. The $^{44}$Ti/$^{44}$Sc-generator*

Radionuclide generators are an alternative production route to reactors and cyclotron. They exploit radiochemical equilibria (transient or secular) between mother and daughter isotope. This means that the mother isotope has a half-life much greater than or approximately equal to 10 times longer than the half-life of the daughter usable for imaging. As mother and daughter are isotopes of different elements, they are present in different chemical forms and can be relatively easily separated chemically.

Beside the $^{99}$Mo/$^{99m}$Tc-generator, which is still the working horse in nuclear medicine, the relevance of the $^{68}$Ge/$^{68}$Ga-generator continues to increase with recent developments of new potent $^{68}$Ga-radiopharmaceuticals for PET imaging. Apart from the cyclotron, scandium-44 can also be produced via $^{44}$Ti/$^{44}$Sc-generator system. Just like the $^{68}$Ge/$^{68}$Ga-generator, there is a secular equilibrium between the long-living mother and the short-living daughter nuclide. Titanium-44 decays via electron capture ($t_{1/2}$ = 59 ± 2 a) [60] into the ground state of scandium-44 which transforms to the stable calcium isotope calcium-44 emitting a positron.

First studies on the design of a $^{44}$Ti/$^{44}$Sc-generator were conducted in the 1960ies and 70ies excluding pharmaceutical aspects [32, 35, 61, 62]. A first 185 MBq $^{44}$Ti/$^{44}$Sc-generator designed for radiopharmaceutical use was described in the last decade [31] as well as a suitable post-processing [40]. An initial preclinical proof of concept study could show that scandium-44 is able to radiolabel a clinical relevant precursor (DOTA-TOC) leading to a stable radiopharmaceutical in good yields as well as the suitability of the generator and post-processing for this purpose [38]. Furthermore, a first clinical application of [$^{44}$Sc]Sc-DOTA-TOC, radiolabeled with generator-derived scandium-44, was conducted to proof the high potential of the radionuclide for PET imaging [30].

First challenge in the development of the $^{44}$Ti/$^{44}$Sc-generator is the high-yield production of titantium-44 via accelerated particles. Up to now, all attempts building a $^{44}$Ti/$^{44}$Sc-generator described in the literature use the $^{45}$Sc(p,2n)$^{44}$Ti-process, although cyclotrons of high positron flux are necessary, to obtain titanium-44 in relatively low radioactivity yields [31, 32, 35, 61–63]. Before titanium-44 can be used separation from the target material and subsequent purification from residual metallic contaminants is mandatory.

Generally, for the design of a radionuclide generator, several critical radiochemical parameters have to be considered, such as separation strategy, stability of the generator and type of eluate. In context with the $^{44}$Ti/$^{44}$Sc-generator, this means a separation strategy is needed which provides high $^{44}$Sc-elution yields combined with low $^{44}$Ti-breakthrough employing an eluate which is suitable for subsequent radiolabeling in terms of pH, volume and purity. Additionally, this separation strategy should guarantee high long-term stability of the generator. This is of particular importance for the $^{44}$Ti/$^{44}$Sc-generator compared for example to the $^{99}$Mo/$^{99m}$Tc- or $^{68}$Ge/$^{68}$Ga-generators as usage for many years due to the long physical half-life of titanium-44 is possible.

The $^{44}$Ti/$^{44}$Sc-generator system developed by Filosofov et al. uses the properties of $Sc^{III}$ in oxalic as well as hydrochloric acid as basis of an anion-exchange separation strategy [31]. This concept leads to $^{44}$Sc elution yields of 180 MBq in 20 ml 0.005 M $H_2C_2O_4$/0.07 M HCl accompanied by a $^{44}$Ti breakthrough of 90 Bq representing a separation factor of $2 \times 10^6$ [31]. Long-term stability of the generator is ensured by a reverse elution mode which is needed to

provide high retention of titanium-44 on the column [31]. This concept leads to a generator design providing scandium-44 in stable yields without significant $^{44}$Ti-breakthrough since approximate 10 years.

As volume, pH and eluent composition of the 180 MBq $^{44}$Ti/$^{44}$Sc generator are not suitable for subsequent radiolabeling, for example, peptides for clinical application, an efficient post-processing strategy in analogy to the post-processing approach of $^{68}$Ge/$^{68}$Ga generators was developed [40, 64, 65]. This post-processing includes reduction of the volume of $^{44}$Sc solution, optimization of pH for subsequent radiolabeling as well as further purification from metal contaminants disturbing the complex formation by utilizing a cation exchange column. Finally, ~ 90% of chemically and radiochemically highly pure scandium-44 can be recovered in 3 ml 0.25 M ammonium acetate (pH = 4) with less than 7 Bq $^{44}$Ti-breakthrough within 10 min ready for following radiolabeling reactions [21, 38, 40].

### 2.2. Synthesis of [$^{44}$Sc]Sc-PSMA-617

DOTA is used as bifunctional chelator in PSMA-617 (cf. **Figure 1**) requiring elevated temperatures for complex formation. Commonly DOTA-based radiopharmaceuticals are prepared using 95°C; therefore, it was evident to choose this as radiolabeling temperature for generator as well as for cyclotron produced scandium-44 [21, 25].

Due to the low activity obtained from the $^{44}$Ti/$^{44}$Sc-generator, evaluation of the influence of precursor amount and reaction time on radiochemical yield resulted in apparent molar activities of 6.50 ± 0.76 MBq/nmol [21] while values of 5–10 MBq/nmol using cyclotron produced scandium-44 are possible [20].

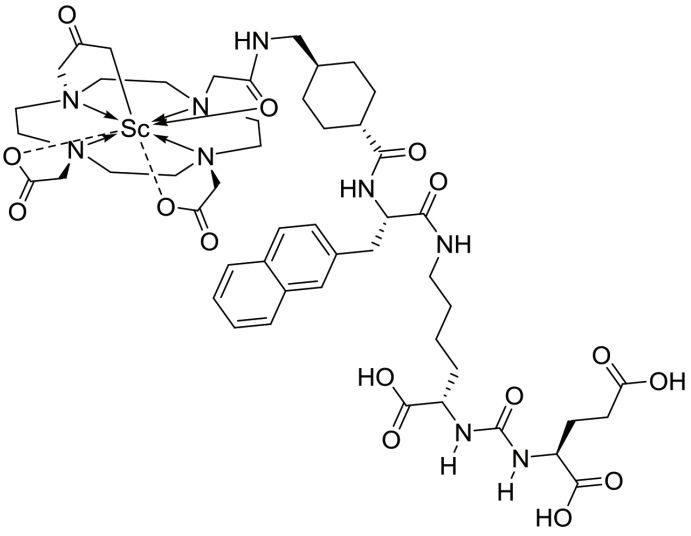


**Figure 1.** Putative structure of [$^{44}$Sc]Sc-PSMA-617.

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With regard to the reported radiochemical yields of >97% [20, 21], it seems not necessary to evaluate a purification method. Nevertheless, removal of unwanted ions (e.g., acetate ions, uncomplexed $^{44}Sc^{3+}$) from the crude product solution is of interest especially with a view to clinical application. The purification method of choice is solid phase extraction. This cheap and easy method is commonly used when it is necessary to purify radiopharmaceuticals. Solid phase extraction with C-18 cartridges was suitable for further purification. After equilibration of the cartridge, almost quantitative retention of [$^{44}$Sc]Sc-PSMA-617 on the cartridge and product recovery with >90% efficacy is possible [21].

### 2.3. Preclinical evaluation

The evaluation of the logD values of the $^{68}$Ga-, $^{44}$Sc- and $^{177}$Lu-complexes and [$^{68}$Ga]Ga-PSMA-11 revealed that the values are in the same range for the PSMA-617 complexes and reduced for [$^{68}$Ga]Ga-PSMA-11(cf. **Table 4**) [20].

The presence of metal cations like $Fe^{3+}$ or other chelators can cause a release of the radionuclide from PSMA-617. As this is a crucial factor for later use as a radiopharmaceutical stability of [$^{44}$Sc]Sc-PSMA-617 against transmetallation, transchelation as well as its stability in human serum and in final formulation was investigated. To determine the stability in the presence of relevant metal cations, those typically present in vivo ($Ca^{2+}$, $Fe^{3+}$, $Mg^{2+}$), at levels significantly higher compared to normal in vivo levels, were chosen. Transchelation was determined against DTPA and EDTA, two chelators forming scandium complexes already at room temperature. In all stability experiments more than 95% of [$^{44}$Sc]Sc-PSMA-617 remained intact even after 24 h incubation [21]. (cf. **Table 3**).

Eppard et al. as well as Umbricht et al. determined the binding affinity of $^{nat}$Sc-PSMA-617 but by different methods and cell lines [20, 21]. Due to the differences in the experimental set up, the results are not directly comparable. Nevertheless, there are similarities. Binding affinity to the target were for [$^{44}$Sc]Sc-PSMA-617 and [$^{177}$Lu]Lu-PSMA-617 in the same range cf. (**Table 4**). Similar results could be observed for the internalization of the radioligands. Uptake was comparable for all compounds without any significant differences within the

| Time (h) | % intact [$^{44}$Sc]Sc-PSMA-617 ± SD | | | | | | |
|---|---|---|---|---|---|---|---|
| | $Ca^{2+}$ | $Mg^{2+}$ | $Fe^{3+}$ | EDTA | DTPA | NaCl | Human serum |
| 0.5 | 98.0 ± 0.0 | 98.7 ± 0.5 | 97.3 ± 0.9 | 96.7 ± 0.1 | 96.7 ± 1.2 | 98.7 ± 0.5 | 98.7 ± 0.5 |
| 1 | 98.3 ± 0.5 | 98.3 ± 0.5 | 98.0 ± 0.8 | 97.3 ± 0.1 | 97.7 ± 0.5 | 98.0 ± 0–8 | 98.0 ± 0.8 |
| 2 | 97.0 ± 0.1 | 98.0 ± 0.8 | 98.0 ± 0.8 | 97.3 ± 0.1 | 97.0 ± 0.8 | 97.7 ± 1.3 | 98.0 ± 0.4 |
| 4 | 97.0 ± 1.4 | 97.7 ± 0.5 | 96.7 ± 0.5 | 97.3 ± 0.1 | 96.7 ± 0.5 | 97.3 ± 0.5 | 97.0 ± 0.8 |
| 24 | 96.7 ± 0.8 | 97.2 ± 0.8 | 95.0 ± 1.4 | 95.9 ± 1.2 | 95.1 ± 0.8 | 96.0 ± 0.8 | 96.3 ± 0.9 |

**Table 3.** Stability of [$^{44}$Sc]Sc-PSMA-617 at 37°C in the presence of different metal cations and in the presence of DTPA and EDTA, at $10^{-2}$ M concentration respectively (n = 3).

| | Log D | Relative PSMA-binding affinity | |
|---|---|---|---|
| | | LNCaP cells | PC-3 PIP cells |
| [$^{44}$Sc]Sc-PSMA-617 | −4.21 ± 0.04 | 1.47 | 1.18 |
| [$^{177}$Lu]Lu-PSMA-617 | −4.18 ± 0.06 | 1 | 1 |
| [$^{68}$Ga]Ga-PSMA-617 | −4.30 ± 0.10 | 1.08 | 0.54 |
| [$^{68}$Ga]Ga-PSMA-11 | −4.82 ± 0.07 | 0.58 | 0.45 |

**Table 4.** Log D (n = 3–5) and relative PSMA-binding affinity as the inverse molar ratio of the average $K_D$ values as determined in cell studies with LNCaP cells [21] and PC-3 PIP cells [20] according to Reddy et al. [66].

experimental set up [20, 21]. Additionally, it was possible to prove PSMA-specific uptake/internalization for all radioligands used employing a PC-3 PIP/flu tumor model [20, 21].

Umbricht et al. performed biodistribution and small animal imaging studies in PC-3 PIP and PC-3 flu tumor-bearing mice directly comparing [$^{44}$Sc]Sc-PSMA-617 with [$^{177}$Lu]Lu-PSMA-617, [$^{68}$Ga]Ga-PSMA-617 and [$^{68}$Ga]Ga-PSMA-11 under the same in vivo conditions [20]. The study confirmed comparable in vitro behavior, which was expected due to similar coordination behavior of scandium-44 and lutetium-177 [20, 48]. The similar chemical behavior of the two nuclides is also evident in vivo in the pharmacokinetics of the radiopharmaceuticals. [$^{44}$Sc]Sc-PSMA-617 and [$^{177}$Lu]Lu-PSMA-617 revealed a largely identical biodistribution within in the investigated period of time [20]. Along with the advantage of the longer half-life of scandium-44, enabling late-time imaging, the increasing tumor-to-background ratio over time can be exploited [20]. Additional comparison with the [$^{68}$Ga]Ga-PSMA-617 confirmed small differences in the pharmacokinetics of [$^{68}$Ga]Ga-PSMA-617 and [$^{177}$Lu]Lu-PSMA-617 explainable with the different coordination chemistry of gallium and lutetium [20].

### 2.4. Synthesis and quality control for human use

The pharmacopeia contains recognized pharmaceutical rules on the quality, testing, storage and labeling of medicinal products and the substances, materials and methods used in their manufacture and testing. It is legally binding [21].

As scandium-44 is a new isotope for human PET application, there is no monograph in the European or another pharmacopeia available for the preparation of scandium-44 or $^{44}$Sc-radiopharmaceuticals. Therefore, quality control was performed based on the monograph for [$^{68}$Ga]Ga-DOTATOC of the European Pharmacopeia [67].

With respect to the use of generator-derived scandium-44, special attention has to be paid to the quality control of the titanium-44 content in the final formulation.

To ensure the quality of [$^{44}$Sc]Sc-PSMA-617, the radiolabeling procedure was modified for patient application. Since only a maximum of 180 MBq scandium-44 is available via the generator per elution and the time from the beginning of the generator elution to the injection to the patient is 3–4 h, it was necessary to guarantee high and stable radiochemical yields. To achieve this, the amount of precursor was increased to 38.4 nmol, and 9 vol% ethanol

was added to the radiolabeling mixture. Ethanol has two tasks: to improve radiolabeling efficacy [68] and to prevent radiolysis in the initial radiolabeling mixture. Its use as scavenger is very important to ensure radiochemical purity as radiolysis by-products can cause undesired and serious side effects while their removal is time-consuming and complicated. Additionally, C-18 purification was performed by default. This step removes potentially remaining $^{44}$Ti-breakthrough, uncomplexed scandium-44 as well as ammonium acetate buffer prior to final formulation of the radiopharmaceutical. Although this step extends synthesis time, its contribution to ensure radiochemical and especially radionuclidic purity is very important. With respect to the use of generator-derived scandiuim-44, the $^{44}$Ti-breakthrough was of major interest. During process set-up, it was even tested twice, in the radiolabeling mixture and final formulation. It was measured not earlier than 120 h after synthesis in a γ-spectrometer at 67.9 and 78.3 keV. Titanium-44 was not traceable in any of the quality control samples.

Due to the limited activity derived from the $^{44}$Ti/$^{44}$Sc-generator system, the apparent molar activity was 3.05 ± 0.36 MBq/nmol at time of calibration (end of synthesis) which is considerably lower compared to [$^{68}$Ga]Ga-PSMA-11 (14–355 MBq/nmol) or [$^{68}$Ga]Ga-DOTA-TOC (4–72 MBq/nmol).

Parameters checked during the quality control procedure were listed in **Table 5**.

Due to the nature of radiopharmaceuticals sterility, breakthrough and content of long living radionuclides could not be determined before release of the final radiopharmaceutical. Therefore, only a preliminary release was possible. Final release of the respective batch was performed with receipt of the last test results.

| | **Method** | **Acceptance criteria** |
|---|---|---|
| Volume activity | Dose calibrator | 5–15 MBq/ml |
| Visual appearance | Optical | Clear, colorless |
| Drug Identity | Radio-HPLC | 11.3 ± 0.4 min |
| Nuclide identity | γ-Spectroscopy | 511 ± 25 keV |
| | Decay measurements | 3.97 ± 0.2 h |
| pH | Indicator strip | 4–8.5 |
| Apparent molar activity | Calculation | 0.7–8 MBq/nmol |
| Radiochemical purity | Radio-HPLC/Radio-TLC | ≥ 95% |
| Long living nuclides | γ-Spectroscopy | Yes/No |
| Breakthrough | γ-Spectroscopy | < 0.001% |
| Filter integrity | Bubble point | > 3447 mbar |
| Endotoxins | LAL-test | < 17.5 IU/ml |
| Sterility | According Ph. Eur. | Sterile |

**Table 5.** Parameters checked during quality control with acceptance criteria and average value measured.

## 3. Part II: Dosimetry

Theranostics and personalized medicine in oncology are in need for highly sensitive and specific diagnostic PET probes that may be radiolabeled with therapeutic radionuclides [18]. It is assumed that diagnostic PET agent distribution is more appropriate for prediction of therapeutic dose increasing therapeutic outcome [18]. Among the several matched pairs for imaging and therapy used in nuclear medicine, focus is on the PET nuclides gallium-68 and scandium-44 as imaging counterpart for lutetium-177.

### 3.1. Methodology

For the first clinical application, five men with progressive mCRPC enrolled for [$^{177}$Lu]Lu-PSMA-617 therapy received [$^{44}$Sc]Sc-PSMA-617 for PET imaging (cf. **Table 6**) [21, 69, 70].

The study protocol stipulates PET/CT imaging starting with a dynamic PET scan of abdomen with kidneys in the field of view (FOV) followed by a low dose CT scan and three static whole-body scans from skull to mid-thigh acquired 45 minutes, 2 h and 19.5 h post injection with preceding low-dose CT. Quantitative analysis was performed visually to identify organs of increased tracer uptake as source organs for further dosimetric calculations. Residence times, organ-absorbed doses (mSv/MBq) as well as effective doses were calculated during quantitative analysis [21, 69, 70] and the maximum permissible activity as well as the maximum number of therapy cycles (6 GBq per cycle) which can be administered were determined [70].

### 3.2. First in-human studies

Following the promising preclinical results, Eppard et al. conducted a first-in-human application [21, 69, 70].

In all patients, PSMA-positive metastases were detectable by [$^{44}$Sc]Sc-PSMA-617 PET/CT applying a single dose of 50.45 ± 9.25 MBq. Visual comparison with images from previous [$^{68}$Ga]Ga-PSMA-11-PET/CT those from [$^{44}$Sc]Sc-PSMA-617 PET/CT were found to

| Patient no. | Age | Weight (kg) | Hematocrit | Injected activity (MBq) | Injected activity (MBq/kg) | PSA (ng/ml) |
|---|---|---|---|---|---|---|
| 1 | 70 | 78 | 0.33 | 50.00 | 0.64 | 453.00 |
| 2 | 72 | 80 | 0.30 | 62.23 | 0.78 | 26.00 |
| 3 | 67 | 70 | 0.39 | 39.61 | 0.57 | 7.20 |
| 4 | 70 | 80 | 0.30 | 50.00 | 0.63 | 139.00 |
| 5 | 67 | 104 | 0.29 | 48.95 | 0.47 | 3000.0 |
| Mean | 69 | 82.4 | 0.32 | 50.16 | 0.62 | |
| SD | 2.2 | 12.76 | 0.04 | 8.04 | 0.11 | |

**Table 6.** Details of study population [21, 69, 70].

be at least equal at a significantly reduced dose. Direct comparison of [$^{68}$Ga]Ga-PSMA-11 and [$^{44}$Sc]Sc-PSMA-617 PET/CT images as well as planar scintigraphy and SPECT/CT of [$^{177}$Lu]Lu-PSMA-617 in one patient is depicted in **Figure 2**.

Due to the longer half-life of scandium-44, patient management could become more flexible through its use allowing PET/CT imaging several hours post injection (**Figure 3**) [20]. Indeed using low doses still and late time point imaging still enables detection of lesions while accumulated activity in urinary tract or kidney is no longer observed [21]. Qualitative detection of PSMA-positive lesions is feasible due to increased tumor-to-background ratios and resulting improved image contrast [21].

Khawar et al. reported estimated residence times (MBq-h/MBq) to be prolonged in the liver followed by the kidneys, urinary bladder, bone marrow and rest of organs compared with [$^{68}$Ga]Ga-PSMA-617 [69]. Also, the study revealed that kidneys (3.19E-01 mSv/MBq;

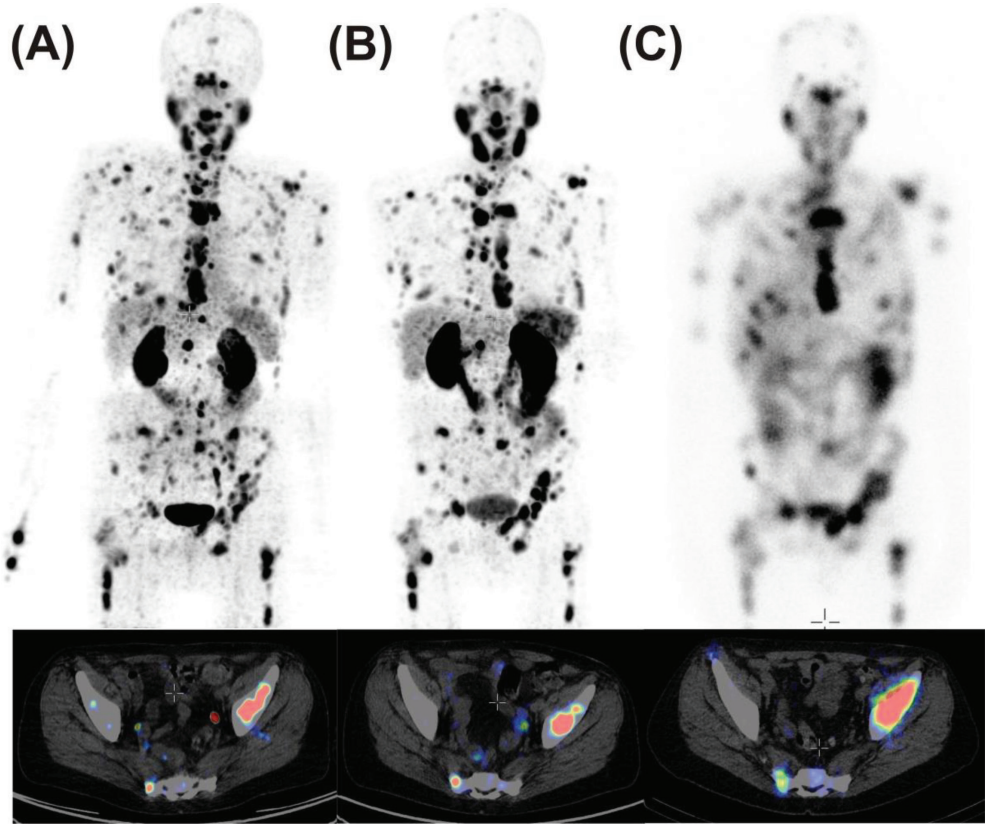


**Figure 2.** Maximal intensity projection (top) and representative slice (bottom) of PET/CT examination of a 70-year-old patient suffering of mCRPC with high tumor load using (A) [$^{44}$Sc]Sc-PSMA-617 (50 MBq, 60 min p.i.), and (B) [$^{68}$Ga]Ga-PSMA-11 (120 MBq, 60 min p.i.). (C) On the right-hand side, the planar scintigraphy (top) and a representative slice of the post-therapy SPECT/CT scan, about 24 h after application of 6.7 GBq of [$^{177}$Lu]Lu-PSMA-617 are shown [21].

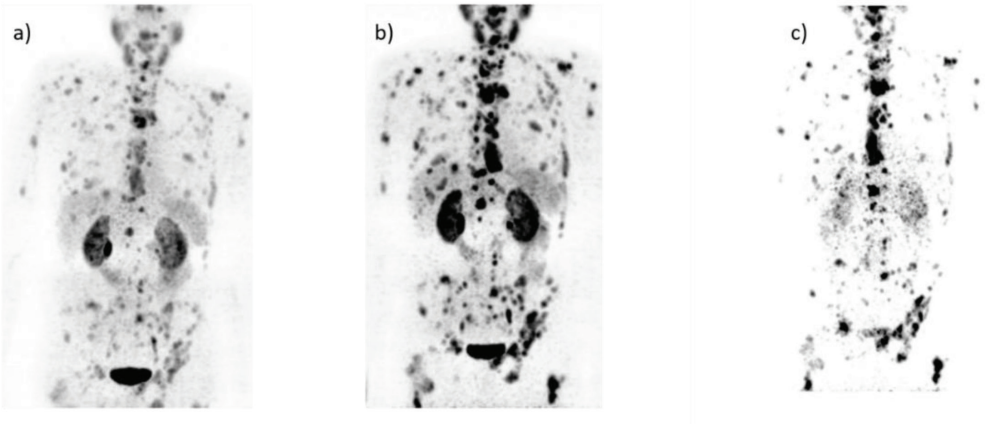


**Figure 3.** PET/CT whole body images at different time points p.i. using [$^{44}$Sc]Sc-PSMA-617: (A) 30 min, (B) 120 min, and (C) 19 h [21].

range: 1.78 E-01-4.88E-01 mSv/MBq) are the critical organs at risk receiving the highest dose followed by the urinary bladder wall, spleen, salivary glands, liver and small intestine while bone marrow dose was less and consequently not included in organs at risk for therapeutic application [69]. These findings are consistent with the results for small PSMA ligands of previous studies [71, 72]. Overall, the study confirmed absorbed doses to be higher for [$^{44}$Sc]Sc-PSMA-617 than for [$^{68}$Ga]Ga-PSMA-617, [$^{68}$Ga]Ga-PSMA-11, [$^{68}$Ga]Ga-PSMA-I&T but less than [$^{124}$I]I-PSMA [69]. Also the mean effective dose was found to be higher than [$^{68}$Ga]Ga-PSMA-617, [$^{68}$Ga]Ga-PSMA-11, [$^{68}$Ga]Ga-PSMA-I&T but less than [$^{124}$I]I-PSMA [69, 72].

In a follow-up study, Khawar et al. used [$^{44}$Sc]Sc-PSMA-617 PET/CT for pre-therapeutic dosimetry estimating the organ doses of [$^{177}$Lu]Lu-PSMA-617 administered [70]. This was performed by mathematical exploration of pharmacokinetics of [$^{44}$Sc]Sc-PSMA-617 to that of [$^{177}$Lu]Lu-PSMA-617. As preclinical in vitro and in vivo studies proofed better correlation between [$^{44}$Sc]Sc-PSMA-617 and [$^{177}$Lu]Lu-PSMA-617 as compared to $^{68}$Ga-PSMA agents, the authors assumed that dosimetric analysis from 19.5 h imaging data of [$^{44}$Sc]Sc-PSMA-617 could be converted into 6.7 d imaging data for [$^{177}$Lu]Lu-PSMA-617 [20, 70]. Total activity (MBq) in source organs and whole body from reconstructed images of dynamic data, and three static whole body PET/CT images were decay corrected back to time of injection using scandium-44 half-life and then forward decay corrected using half-life of lutetium-177 for calculation [70].

**Table 7** shows the mean residence times (MBq-h/MBq) for [$^{44}$Sc]Sc-PSMA-617 and based on [$^{44}$Sc]Sc-PSMA-617 pharmacokinetics for [$^{177}$Lu]Lu-PSMA-617 [69, 70].

Also for [$^{177}$Lu]Lu-PSMA-617, kidneys appeared to be the organ at risk (mean absorbed dose 0.44 mSv/MBq) followed by the salivary glands, liver, small intestine, spleen and urinary bladder wall [70]. The mean bone marrow absorbed dose was reported to be 0.05 mSv/MBq,

| PT No | [44Sc]Sc-PSMA-617 | | [177Lu]Lu-PSMA-617 | |
|---|---|---|---|---|
| | Mean± | SD | Mean± | SD |
| Organs | | | | |
| Salivary glands | 0.03± | 0.027 | 0.24 | 0.21 |
| Kidneys | 0.24± | 0.109 | 1.51 | 0.48 |
| Liver | 0.35± | 0.263 | 4.46 | 1.72 |
| Spleen | 0.07± | 0.031 | 0.18 | 0.07 |
| Small Intestine | 0.05± | 0.029 | 0.63 | 0.37 |
| Bone marrow | 0.09± | 0.047 | 0.52 | 0.69 |
| Urinary bladder contents | 0.18± | 0.195 | 0.33 | 0.32 |
| Remainder of body | 1.82 | 0.684 | 46.58 | 16.04 |

**Table 7.** Mean residence times (MBq-h/MBq) for [44Sc]Sc-PSMA-617 and estimated for [177Lu]Lu-PSMA-617 on basis of [44Sc]Sc-PSMA-617 pharmacokinetics [69, 70].

and the mean whole body dose was 0.08 mSv/MBq [70]. These findings are comparable with literature [11, 13, 17, 19]. Total dose (Gy) per cycle administered lies in a range from 2 till 3.26 Gy although applying the same therapeutic activities [70]. Due to the use of 3D instead of usual 2 D dosimetric analysis, it was found that it is possible to administer a mean dose of 52 Gy to reach a dose limit of 23 Gy [70] which is significantly higher than reported before with 30 Gy [13].

All together both studies proved that dosimetry using [44Sc]Sc-PSMA-617 PET/CT is possible applying a protocol which could be implemented in clinical daily routine.

## 4. Conclusion

Recent studies demonstrated the high potential of [44Sc]Sc-PSMA-617 for PET imaging in a preclinical as well as a clinical setting where it revealed more similar characteristics to [177Lu]Lu-PSMA-617 than the routinely used [68Ga]Ga-PSMA-11 [20, 21].

While images at early time points are comparable with those of [68Ga]Ga-PSMA-11, the advantages of scandium-44 over gallium-68 show up at late time points due to its longer half-life. Enabling delayed image acquisition would simplify patient management at improved image quality and allows improved pre-therapeutic dosimetry for therapy with [177Lu]Lu-PSMA-617. Especially for pre-therapeutic dosimetry scandium-44 would be beneficial as implementation in the clinical setting is uncomplicated, and there is no need for patient hospitalization. Together with the possibility transporting scandium-44 and 44Sc-radiopharmaceuticals further routes to radiopharmaceutical institutions without option for in-house production scandium-44 could make a significant contribution to patient care even in remote areas.

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Chapter 4

# Bipolar Endoscopic Enucleation of Big Benign Prostate Enlargement

Wai Hee Steve Chan, Chi Fai Kan and
Churk Fai Trevor Li

**Abstract**

Large benign prostatic enlargement (BPE) has been a major health problem and the surgical management could be technically challenging to urologists due to the limitation of conventional monopolar transurethral resection of prostate. Bipolar endoscopic enucleation of prostate aimed to remove the adenoma of BPE by stepwise adenoma devascularization and maximal adenoma removal through minimally invasive surgery. In this chapter we described the general principle, the surgical techniques of bipolar endoscopic enucleation and the related modifications of the technique in the recent years. As compared with open prostatectomy, bipolar endoscopic enucleation avoided the wound complications but achieved similar functional outcome. Bipolar endoscopic enucleation also allowed much more adenoma removal comparing with transurethral resection of the prostate. Unlike Holmium laser or thulium laser enucleation of the prostate, the required instruments for bipolar endoscopic enucleation of the prostate were familiar and more readily available to most urologists.

**Keywords:** benign prostatic hyperplasia, bipolar, enucleation, plasmakinetic, transurethral surgery

## 1. Introduction

Benign prostatic hyperplasia (BPH) has been a common and important health condition in the modern society. With the aging population, benign prostatic obstruction (BPO) can affect the patients with different degree of bothersome lower urinary tract symptoms or the associated complications. Transurethral resection of the prostate has been the gold standard treatment

for benign prostatic obstruction (BPO) with prostate volume 30–80 gm [1]. However, despite its minimally invasive nature and more advanced endoscopes, large benign prostatic enlargement especially over 80 gm remains challenging to urologists due to the increased morbidities related to glycine over-absorption during prolonged operation and transurethral resection of the prostate can resect up to 30–53% of the prostate volume only, leading to problems related to inadequate resection e.g. persistent retention of urine in retention patients and recurrent symptoms [1, 2]. Open prostatectomy provides effective treatment for prostate glands larger than 80 gm through more thorough adenoma removal but yet being most invasive comparing the currently available endoscopic enucleation treatment [1, 3]. However, there were associated problems like wound related complications, prolonged post-operative catheterization and risks of severe hemorrhage [3–6].

Hiraoka described the first endoscopic enucleation of the prostate through monopolar current system in 1983 [7]. However not until the development of model endoscopy system, Holmium:YAG laser, bipolar plasmakinetic system and morcellator, endoscopic enucleation was popularized in the urology field [8]. Gilling reported the technique and outcome of Holmium laser enucleation of the prostate in 1998 [9] but the technique has not been widely adopted due to the learning curve of the procedure and the requirement of high-powered Holmium:YAG laser generator and morcellator.

With the development of bipolar plasmakinetic system in transurethral surgery, transurethral resection can be performed with normal saline irrigation with provides better patient safety and comparable outcome with monopolar system [1]. Neill described the result of his randomized controlled result comparing plasmakinetic enucleation of the prostate with Holmium laser enucleation with Gilling's group in 2006 [9]. Bipolar endoscopic enucleation of prostate is further popularized by Prof Liu CX's group [10] which presented their experience in 1100 patients in 2003–2009, using the technique with only the bipolar transurethral surgery system without the use of morcellator. In the last 15 years, bipolar endoscopic enucleation of the prostate has been reported in many centers with different bipolar transurethral systems, electrodes, modified resection devices and tissue removal technique [3–8, 10–21], so that there was no single unified terminology to describe this technique. In this chapter the term "bipolar endoscopic enucleation of prostate" [12] is used to highlight to key component of this transurethral technique [10–15] and to concur with the term "endoscopic enucleation of the prostate" used in the current guideline in European Association of Urology [1].

## 2. Surgical technique of bipolar endoscopic enucleation of prostate

### 2.1. Patient preparation

The indications of bipolar endoscopic enucleation of prostate follow the principle of benign prostate enlargement treatment [1]. The patient would have pre-operative urine culture be performed and treated accordingly to prevent peri-operative urosepsis [22]. Transrectal ultrasound of prostate is recommended in addition to a regular digital rectal examination to evaluate the size of the prostate to avoid prostate size underestimation and the operating surgeons can have a mental image about the shape of the prostate under treatment [1]. This is especially

recommended for surgeons at their initial learning curves to measure the prostate size which provides an insight of anticipated difficulty especially in huge prostates. Oral anticoagulant therapy and/or platelet aggregation inhibitors would be stopped pre-operatively according to the patient's medical condition or regional medical guidelines, though it has been reported that these agents can be continued peri-operatively without excessive increase in transfusion rate and clot retention [16, 23].

### 2.2. Operative description of bipolar endoscopic enucleation of prostate

Our technique and experience of bipolar endoscopic enucleation of prostate has previously been reported [12]. The patient is put on general or spinal anesthesia with Lloyd-Davis position or lithotomy position. The operation is performed with continuous normal saline irrigation, 60–70 cm above the patient level. Cystoscopic examination of the lower urinary tract is performed to rule out any bladder malignancy or calculus. The ureteric orifice, bladder neck and the verumontanum are identified as the important landmark of bipolar endoscopic enucleation of the prostate.

Enucleation of the adenoma started from just proximal to the verumontanum at 5 and 7 o'clock. It aims to cleave the plane between the adenoma to the surgical capsule just proximal to the external urinary sphincter. The beak of the resectoscope could directly enter this plane through blunt dissection or an incision could be made over the urethral mucosa to the surgical capsule to start the enucleation but it may result in more bleeding and obscure the vision [18, 19]. This landmark is easily identifiable and the thickness of tissue that required to be cut is the thinnest. The surgeon should be able to visualize the whitish smooth surgical capsule of the prostate soon after opening up the urethral mucosa here. For bilobar BPE patient, enucleation is started just proximal to the verumontanum (**Figure 1**). Then, the plane between

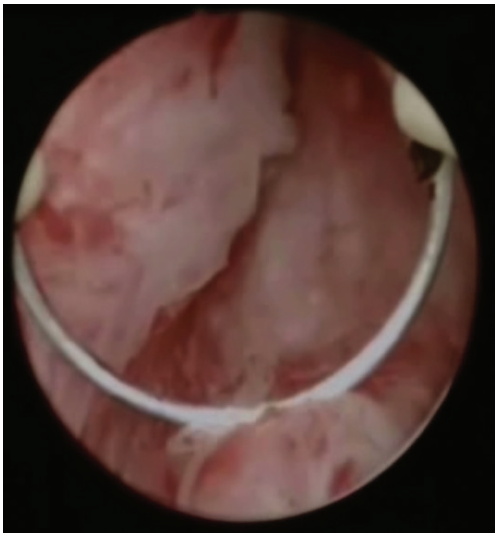

**Figure 1.** Incision of the urethral mucosa just proximal to verumontanum in case of enucleating bilobar enlarged prostate.

the adenoma and the capsule is developed by the beak of the resectoscope or by the bipolar electrode (**Figure 2**), depending on the preference of the surgeon and the available electrode. The distal mid lobe is dissected in retrograde fashion to the bladder neck. The blood vessels are coagulated by the bipolar electrode and the adhesive fibers are cut to open up the plane. The procedure is continued till the circular fiber of the bladder neck is identified (**Figure 3**). The bladder mucosa is incised to enter the bladder at 5 or 7 o'clock. Caution should be taken to dissect the posterior mid gland from the surgical capsule along the contour of the prostate posterior surface, so as to avoid perforation of the prostatic capsule and undermining the bladder neck at 6 o'clock.

The plane is further developed laterally with the suppling vessels coagulated. Both lateral lobes are enucleated laterally (**Figure 4**) to reach the 11 o'clock and 1 o'clock of the anterior fibromuscular stroma, where the adenoma is usually adhered more densely than the other region [17]. The attachment at 12 o'clock allows the adenoma be resected in the prostatic fossa rather than free floating inside the bladder.

Some urologists prefer to have enucleation of the prostate by starting from 5 or 7 o' clock proximal to the verumontanum and then bluntly dissected the adenoma laterally. The bladder was entered at 11 and 1 o'clock of the bladder neck to avoid entering the bladder over the trigone area. The anterior fibromuscular stroma at 12 o'clock was joined through the bilateral dissection plane and the adenoma was left attached to the bladder neck to facilitate adenoma resection.

After majority of the adenoma is devascularized, the adenoma is resected from the bladder neck by the loop electrode in an almost bloodless manner (**Figure 5**). The prostate chips are removed by Ellik's evacuator. As in usual bipolar transurethral resection of the prostate, gas

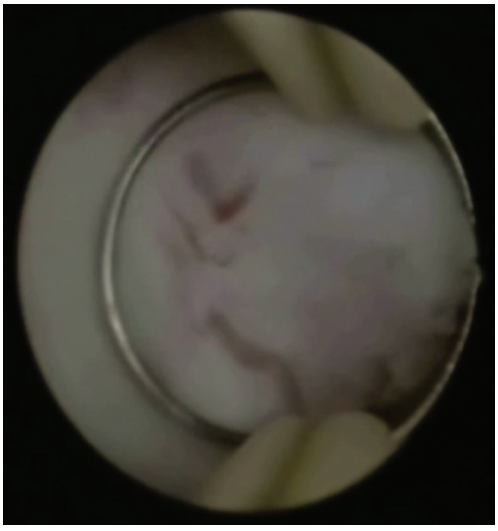

**Figure 2.** Development of the enucleation plane by using the beak and the bipolar electrode. The feeding vessels to the adenoma were coagulated.

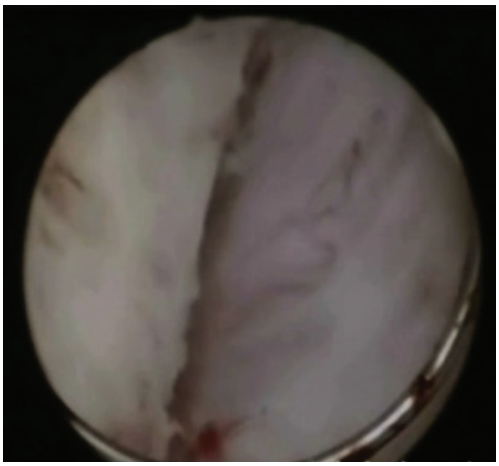

**Figure 3.** The enucleation process is continued till the circular muscle fiber of the bladder is noted.

will be accumulated inside the bladder and the intravesical pressure has been measured to be around 25 mmHg [17]. The increased intravesical pressure may obscure some venous bleeding. Careful hemostasis should be obtained after drainage of thee intravesical gas.

### 2.3. Tips and tricks of the technique of bipolar endoscopic enucleation of prostate

There are different kinds of bipolar transurethral systems reported in literature such as Gyrus PlasmaKinetic (PK) system, Olympus system through SurgMaster™ USE 40 generator

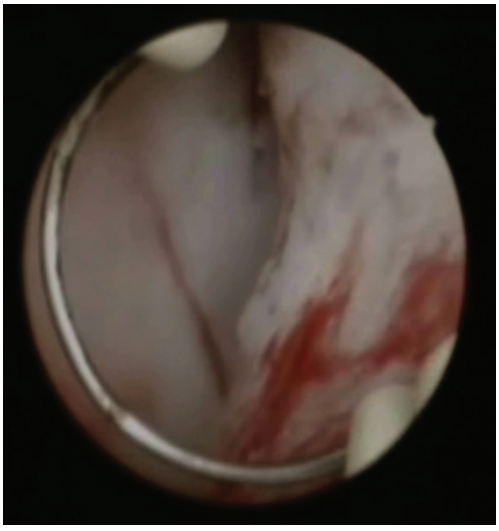

**Figure 4.** Enucleation of the lateral lobe of the adenoma.

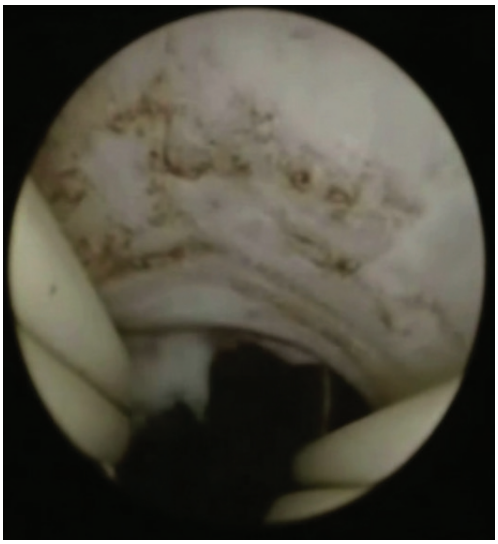

**Figure 5.** Resection of the devascularized adenoma from 6 o'clock from the bladder neck with the scope oriented upwards.

(Olympus Tokyo Japan) and Scanmed Plasmakinetic System (Scanmed, Zhuhai, China) [3, 7–19, 22]. However, it has been shown in that in Quasi-bipolar system which the electrical current is returned to the generator through the outer sheath of the bipolar resectoscope, the urethral stricture rate can be higher if the procedure is prolonged in larger prostate size >70 gm resection [24]. It is postulated that the return current over the out sheath may damage the bulbous urethra and causes an higher incidence of urethral stricture. However, this finding was reported in a single centre's experience [24] and was not observed in other groups' results using similar instruments [10, 19]. There will be some difference in design of the beak of the resectoscope and the strength of the electrode in different bipolar systems. The surgeon should be familarized with their instrument before deciding to use the beak or the electrode for enucleation.

Button electrode has been developed in both Gyrus PK and Olympus system. The button electrode has larger contact surface area and allows easier contact coagulation and vaporization. Button electrode has been used in bipolar endoscopic enucleation of the prostate [14, 15, 23] and it has been shown to provide better hemostasis especially for patients on anti-coagulation therapy [23]. The learning curve is also proposed to be shorter than the conventional bipolar endoscopic enucleation of prostate by using loop electrode [15]. However, these button electrodes are designed as single use items. Extra instruments such as loop electrode or morcellator are required for prostate adenoma resection on top of the use of button electrode. The Japanese group also reported the use of loop electrode with a specially designed spatula for blunt enucleation [13], though it is not readily available in other parts of the world.

In case of gross trilobar enlargement with prominent median lobe, 3-lobe technique can be considered [11, 18]. Incision is made at 5 and 7 o'clock of from the bladder neck to the verumontanum. The median lobe is enucleated and removed first. The procedure is continued with further enucleation of the lateral lobes through the same plane. The continuous normal saline irrigation is improved with the median lobe removed first.

A Chinese group described another enucleation technique to overcome the problem of enucleation of the prostate over the more densely adhered anterior fibromuscular stroma at 12 o'clock [17]. That region was firstly resected by bipolar transurethral resection of prostate down to the surgical capsule. The enucleation of the prostate is then started from verumontanum and then directed laterally to the 10 and 2 o'clock position. The adenoma is left attached to the bladder neck at 6 o'clock to avoid adenoma dislodgement into the bladder.

Despite adequate devascularization of the adenoma after enucleation, resection of the large adenoma with loop electrode can be difficult due to its size and disorientation, especially at the early learning curve. Our group resects the adneoma from 6 o'clock from the bladder neck with the scope oriented upwards, so that the resection of adenoma directed at 12 o'clock will not damage the surgical capsule [12]. Prof Liu utilized both forward and backward movement of the working element to resect the devascularized adenoma, in order to reduce the operative time [11]. Besides using the loop electrode for adenoma resection, morcellator is also used in some centers to reduce the adenoma resection time [13, 25], though caution should be taken to avoid bladder injury by the morcellator.

Although bipolar transurethral system allows the procedure to be safely performed in a longer period of time, it has been a concern if there is over-absorption of normal saline during the enucleation procedure especially with potential capsular perforation. Ran and his colleagues have compared the irrigation fluid absorption volume with bipolar enucleation and bipolar resection technique using 1% ethanol containing saline solution. It is found that there would be around 900 ml fluid absorbed for bipolar endoscopic enucleation with around 70 gm prostate [26] and it was not different from bipolar transurethral resection of the prostate with similar size. Especially in patients with underlying cardiovascular conditions, it is advisable to give frusemide intra-operatively to reduce the chance of fluid overload [11].

## 3. Surgical outcome of bipolar endoscopic enucleation of prostate

### 3.1. Functional outcome

Current literature demonstrated bipolar endoscopic enucleation of prostate could achieve functional outcome comparable to open prostatectomy. Data drawn from bipolar endoscopic enucleation of prostate arm of 5 randomized control trials for prostate size >80 ml [3, 17] showed that bipolar endoscopic enucleation of prostate reduced lower urinary tract symptoms by 83% (76–86%, with reduction of IPSS point 17.6–22.1), improved quality of life (QOL) score by 70% (50–82%), increased mean maximum urine flow (Qmax) by 331% (152–535%, +9.6–21.4 ml/s), and reduced post voiding residual volume (PVR) by 86% (68–93%). Efficacy was maintained for up to 6 years [5].

For perioperative outcomes, it was reported that the resected specimen's weight could reach a mean of 80.4% of the preoperative prostate size. Average operative time was 109 min [3, 5, 6, 17] with a mean prostate size of 111 cc, and this was likely achieved by surgeons that have passed the learning curve. With the use of morcellator operative time could be further shortened, as demonstrated in one randomized control trial [4] the operative time was 87 mins with a mean prostate size of 123 cc.

The randomized controlled trials reported the catheterization time to be 2.3 days, and the average length of stay was 4.2 days. Re-catheterization due to retention ranged from 0 to 4.3%.

### 3.2. Complications

For early complications, transient stress urinary incontinence was reported ranging from 0 to 8.75%. One randomized controlled trial reported early storage urinary symptoms to be 2.1% [17]. Mean hemoglobin drop of 1.16 g/dL with blood transfusion rate ranging from 0 to 6.4%. UTI was reported ranging 3.6–7%. There was a small chance of clot retention 0–1.1%.

For late complications, bladder neck contracture/stenosis was reported to be 0–2.4%, urethral stricture was reported as 2.1–3.75%. There was no permanent incontinence reported in this 5 RCT, and no reoperation for regeneration of adenoma was reported.

### 3.3. Learning curve

Xiong et al. evaluated the learning curve of the initial 100 cases of 2 surgeons. It was reported that the surgeons required 30 operations until a few conversions to conventional bipolar TURP occurred [19]. It also noted that 50 operations were required to achieved a stable surgical efficiency, as measured by mL/minute of tissue being enucleated and resected. This was echoed by another Japanese single surgeon cohort [13], which showed the efficiency improved markedly when the surgeon experience exceeded the initial 50 cases. With the presence of mentor, 40 cases was required to reach plateau in terms of operation or enucleation efficiency in g/min, as shown in one retrospective study [27].

Barriers during the learning curve focused on properly identifying and handling the right plane in the absence of mentorship. The anatomic landmarks that prompt the surgeon to identify the surgical plane mainly include capsule transverse fibers or fiber strands, capsule vessel reticula, capsule prostate calculi [19].

The advantage of bipolar endoscopic enucleation of prostate during the learning curve is that it can be converted to conventional bipolar transurethral resection of prostate, using the same set of instrument with no harm to patients. Though Tracey et al. reported a higher rate of capsular perforation or undermining of the bladder neck in the initial learning curve in up to 8% [28].

## 4. Comparison with other surgical modality for BPH

### 4.1. Open prostatectomy

Bipolar endoscopic enucleation of prostate was most frequently compared with open prostatectomy in the current available literature as open prostatectomy is still be regarded as the gold standard surgical procedure for large benign prostate enlargement. Four randomized control trials were available [3–6]. All these studies showed the functional outcome were similar but bipolar endoscopic enucleation of the prostate improved perioperative parameters in terms of less hemoglobin drop, less transfusion, shorter catheterization time and shorter

length of stay. The wound complications related to open surgery were avoided including wound dehiscence, wound infection and paralytic ileus reported [5]. There was no significant difference in other mid and long term complications in terms of bladder neck stenosis, urethral stricture. In the European Association of Urology guideline 2018, endoscopic enucleation (including bipolar energy) was rated as first recommended choice for treating substantially enlarged prostate ≥80 gm, same as open prostatectomy (previous gold standard), with a more favorable peri-operative safety profile [1].

### 4.2. Bipolar transurethral resection of prostate

Two randomized control trials [4, 17] compared bipolar TURP with bipolar endoscopic enucleation of prostate. The surgical efficacy was higher for bipolar endoscopic enucleation of prostate with more resected weight as compare to bipolar TURP. At 12 month follow-up, persistent significant difference in Qmax, IPSS and QOL was shown in one randomized controlled trial [17] but not for another one [4]. Significantly higher perioperative complications in terms of clot retention, dysuria, re-catheterization, blood transfusion, and reoperation for bipolar TURP were reported in one randomized controlled study [17].

### 4.3. Photoselective vaporization of prostate (PVP)

One prospective cohort compared PVP (160 W LBO green laser system) with bipolar endoscopic enucleation of prostate. It demonstrated that significant improvement of IPSS, QOL, Qmax, PVR and PSA changes in favor of bipolar endoscopic enucleation of prostate in 12 months (mean prostate size 88.3 ml) [21]. There was no difference in terms of perioperative complications and no transfusion was required in both group of patient.

### 4.4. Holmium laser enucleation of prostate (HoLEP)

One small randomized control trial (n = 40) compared HoLEP and bipolar endoscopic enucleation of prostate in medium sized prostate (mean 51 cc) [10]. The author commented bipolar endoscopic enucleation of prostate had more pronounced postoperative irrigation requirement because of reduced visibility and a greater propensity for bleeding as compared with HoLEP. Longer operative time was noted for bipolar endoscopic enucleation of prostate. However, it was still the early infancy of the development in bipolar endoscopic enucleation of prostate on the study period. The result was likely due to the comparison of initial development of bipolar endoscopic enucleation of prostate to more well established HoLEP technique in the study period. Other perioperative parameters/complications are similar without significant difference between both groups.

### 4.5. Thulium laser enucleation of prostate (ThuLEP)

A randomized control trial [20] compared ThuLEP with bipolar endoscopic enucleation of prostate in medium sized prostate (mean 67.1 cc). ThuLEP provided less risk of hemorrhage and shorter catheter time, although the differences may be of little clinical relevance. No statistical differences in complications between the two groups. Assessment at 12-month follow-up showed no difference in urinary parameters between the two groups.

## 5. Conclusion

Bipolar endoscopic enucleation of prostate provides an excellent minimally invasive modality for surgical treatment of large BPE especially for those ≥80 gm. It allowed better functional outcome than transurethral resection and stepwise adenoma devascularization with minimally invasive technique. The instruments were familiar to most urologists and were available in most modernly equipped urology centers. In addition, it allows easy and quick conversion to traditional transurethral resection. The authors believe endoscopic enucleation of the prostate including bipolar energy has replaced open prostatectomy as the standard of care in the surgical management of large BPE.

## Conflict of interest

There is no conflict of interest to be declared by the authors.

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Chapter 5

# Laparoscopic Simple Prostatectomy

Yusuf Ilker Comez

**Abstract**

Benign prostatic hyperplasia (BPH) is the most common benign tumor and cause of urinary retention in middle-aged male patients. Transurethral resection of the prostate (TURP) is the gold standard surgical treatment for benign prostatic obstruction. Although widely performed, TURP is associated with significant morbidity. Open prostatectomy is performed in larger glands, which are more than 80 grams, with higher morbidity. Advances in technology, such as holmium laser enucleation of the prostate (HoLEP) and KTP laser vaporization, are other options that are widely used despite their limitations. Laparoscopic simple prostatectomy (LSP) is a minimally invasive treatment option with equivalent functional outcomes and is useful in larger prostatic adenomas, with low morbidity in experienced hands.

**Keywords:** prostatectomy, adenomectomy, prostatic adenoma, benign prostatic hyperplasia, laparoscopy, minimally invasive, simple prostatectomy

## 1. Introduction

Benign prostatic hyperplasia (BPH) is the most common benign pathology and cause of urinary retention in middle-aged male patients, and its incidence increases with age.

The International Prostate Symptom Score (IPSS) questionnaire is often used to assess patients of BPH [1]. The treatment depends on the severity of the disease. Conservative approach with watchful waiting and the use of systemic drugs that relaxes the smooth muscles of the prostate and bladder neck, resulting in the decrease in the prostate mass volume, may be preferred in the mild cases. When planning surgery, prostate volume and weight as well as the patients' expectations and associated comorbidities should be taken into account.

In patients with failure or inability to tolerate medical treatment, with urinary retention, renal failure secondary to BPH, urinary infections, bladder calculi, or hematuria, surgical intervention should be preferred [2–5].

Transurethral prostate resection (TURP), simple prostatectomy, and transurethral incision of the prostate (TUIP) have been the main surgical treatment options for benign prostate hyperplasia (BPH) for decades. Although TURP is accepted as the gold standard surgical treatment for benign prostatic obstruction and is widely used in all over the world, it has several limitations such as being insufficient in treating large prostates, risk of perioperative bleeding, postoperative transurethral resection (TUR) syndrome, urethral strictures, and at the same time the risk of reoperation requirement [6].

EAU and AUA guidelines recommend open prostatectomy (OP) for the surgical treatment of patients with prostate volumes larger than 80 ml [7, 8]. The advantages of this technique are lower reoperation rates and better clinical outcomes with more patient satisfaction [9]. However, it has also been associated with the need for perioperative transfusion, prolonged hospital stay, higher reoperation rate, urinary infections, and a large abdominal scar effecting the cosmesis [10–12]. Other rare adverse events as clot retention, contraction in the bladder neck, wound infection, and myocardial infarction may also be encountered [13]. Holmium laser enucleation of the prostate (HoLEP) is used in larger adenomas as an alternative to OP with the advantages such as shorter catheterization and hospital stay. However, the technique is not widely used because of the demanding learning curve, complications, and the need for special equipment [6].

The other laser treatment option as an alternative to OP is the GreenLight® KTP laser vaporization that promised better outcomes for large prostate adenomas with successful results [14]. By this technique surgeons achieved shorter catheterization time and hospital stay with perfect hemostasis [14]. However, the absence of definitive pathological result and lack of long-term results were the obstacles for the widespread use of the technique.

With advancements in the technology, minimal invasive methods such as enucleation of the prostate with holmium laser or laparoscopic simple prostatectomy (LSP) began to show off on stage.

LSP is recently accepted as an alternative to open surgery in patients with large prostate glands. However, it is accepted that learning curve of this technique is steep and time-consuming in order to reach to comparable results to OP [15].

In this chapter the benefits, conflicts, and surgical technique of laparoscopic simple prostatectomy are described with the review of the literature.

## 2. The surgical technique for simple laparoscopic prostatectomy

The surgical procedures may be performed either in an extraperitoneal or transperitoneal fashion [16–18].

Adenomectomy can be performed transvesically or by retropubic transcapsular (Millin) technique [19].

### 2.1. Port placement

The laparoscopic simple prostatectomy begins with placement of the trocars either transperitoneally or extraperitoneally [19, 20].

Intubation and nasogastric decompression are applied at supine position. The bladder emptying is performed after insertion of 22-F Foley catheter. Afterward, the spread of the legs to 30° at Trendelenburg position is performed. Both arms are fixed adjacent to the body (**Figure 1A**).

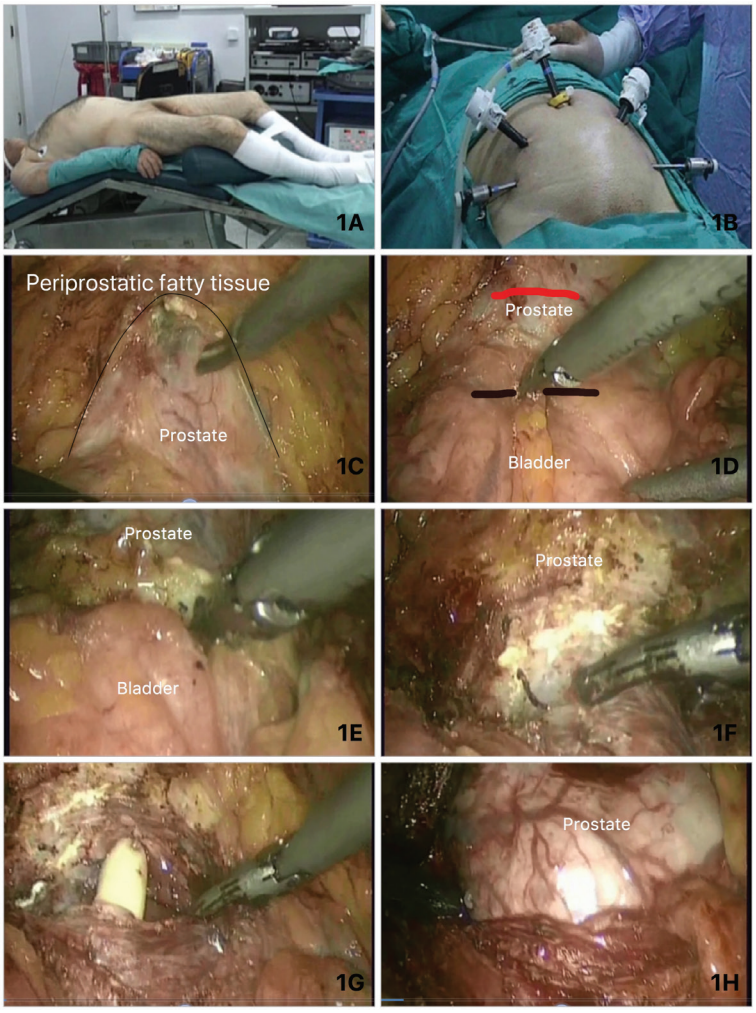


**Figure 1.** (A) The position of the patient for LSP; (B) the port placement for LSP; (C) the defatting the tissue over the prostate capsule; (D) black line shows the incision 1-cm proximal to the prostatovesical junction in transvesical approach; the red line depicts the ventral incision over prostate in retropubic transvesical Millin technique; (E) dissection of the detrussor with harmonic scissors; (F) widening the incision to see both orifices and prostate; (G) intravesical part of the Foley catheter is seen; and (H) the intravesical portion of the prostate can easily be pulled out of the fossa.

*2.1.1. The extraperitoneal approach*

The extraperitoneal approach involves making a 30-mm infraumbilical incision and dissecting down to the anterior rectus fascia. This fascia is incised 30 mm transversely, and after demonstrating the linea alba and rectus muscles, the bellies of the rectus are separated bluntly in the midline. Finger dissection is carried out between the rectus muscle and the peritoneum to form the preperitoneal space, taking care to avoid incidental peritonotomy by applying anterior pressure inferiorly when the posterior rectus fascia disappears below the arcuate line. Linea alba is incised adjacent to symphysis pubis inferiorly. A 12-mm balloon dissector with 10-mm visual optical channel is placed to the preperitoneal space superior to the bladder and the prostate. Anterior rectus fascia defect, near to the port, is closed. Subcutaneous and cutaneous sutures are performed with No.1 silk sutures to avoid gas leakage. The balloon is slowly inflated under direct visualization in the retroperitoneum. In the correct plane, the inferior epigastric vessels are visible ventrally helping to avoid incidental vascular damage. The balloon is deinflated, the 10-mm trocar and a 0-degree optical lens are inserted, and the space is inflated with 10–15 mmHg of $CO_2$. Four additional trocars are inserted under direct visualization. Two 10-mm trocars are placed lateral to the rectus muscle over the line between anterior superior iliac spine and the umbilicus, and two 5-mm trocars are placed 2 cm medial to the anterior superior iliac spines (**Figure 1B**).

*2.1.2. The transperitoneal approach*

The transperitoneal approach is performed with the Trendelenburg position as described previously. A 2-mm incision below the umbilicus is performed. After reaching the rectus fascia, Veress needle is inserted in the peritoneum carefully. After forming pneumoperitoneum, a 10-mm port is replaced with 2-cm port inferior to the umbilicus in the midline between the rectus muscles. The other ports are replaced under direct visualization similar to the retroperitoneal approach. As we reach to the bladder, the peritoneum is incised ventrally to the bladder. By the caudal dissection via peritoneal incision, Retzius space is reached. The next steps of the surgery are similar either extraperitoneal or transperitoneal. As we reach the Retzius space, defatting the tissue over the prostate for better visualization of the prostate and bladder neck is provided (**Figure 1C**).

**2.2. The techniques of dissection**

*2.2.1. The transvesical dissection technique*

The bladder is filled with 200 cc saline. Therefore, careful manipulation of the bladder helps to identify prostatic lobes from the softer bladder wall. If transvesical approach is chosen, a transverse incision is done 2 cm proximally to the prostatovesical junction with harmonic scissors (**Figure 1D**). After transverse cystostomy, one may widen the incision laterally (**Figure 1F**), until the large adenoma can be seen clearly (**Figure 1H**). A grasper can also be used for anterior elevation of the median lobe to see the bladder lumen and orifices clearly (**Figure 2A**). Afterward, the Foley catheter is pulled out, and metal bugi is replaced to lift the prostate superiorly. Adequate vision allows the dissection of the adenoma through a transverse incision distal to the trigone (**Figure 2B** and **C**). The bladder neck is well perfused, and the use of harmonic scissors may be useful to prevent bleeding. Suction and posterior traction by the assistant are

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mandatory. The subcapsular plane can be identified by leaving prostatic capsule posteriorly and elevating the adenoma out of the fossa. In the subcapsular plane, the aspirator is used for blunt dissection, while sharp dissections are made with harmonic scissor (**Figure 2D**). Prostatic tissue is liberated from 6-o'clock to 12-o'clock position in both sides (**Figure 2E** and **F**). In this stage of surgery, the use of suction and harmonic scissors may prevent vision difficulty due to bleeding (**Figure 2G** and **H**). Minor bleedings may be ignored. The pneumoperitoneum may

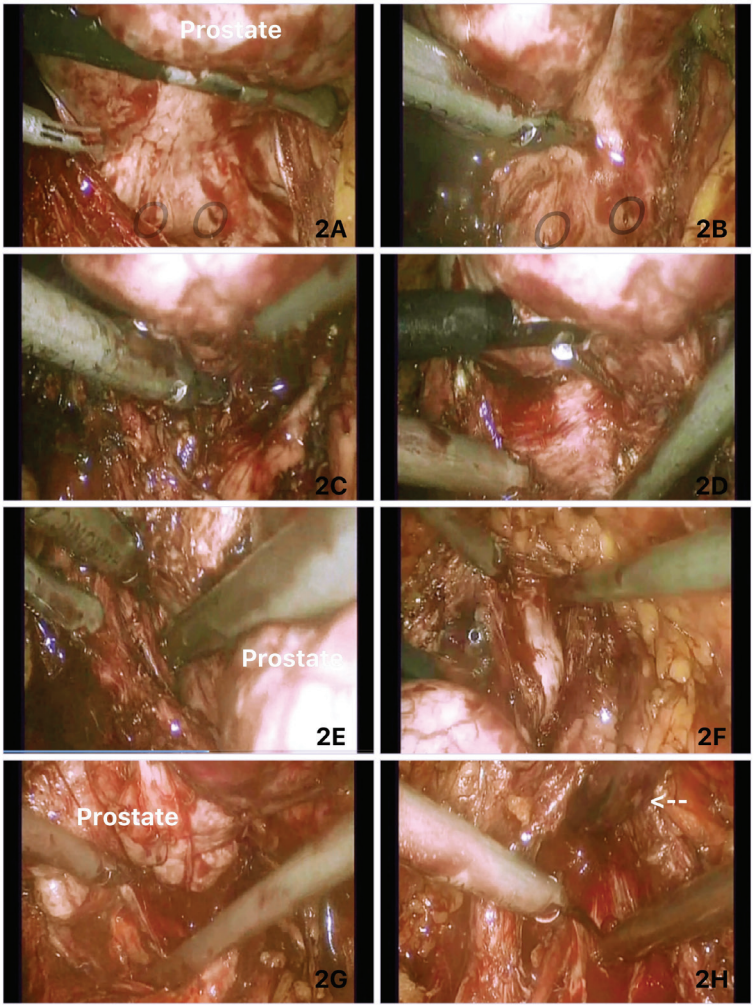


**Figure 2.** (A) a grasper can also be used for anterior elevation of the median lobe to see the bladder lumen and orifices clearly. Both orifices are shown in a black circle; (B) the harmonic dissection of the adenoma through a transverse incision distal to the trigone to enter the subcapsular space; (C) releasing the adenoma; (E) dissection to separate left side of the adenoma from the capsule. A grasper helps for traction while blunt and sharp dissections are held with harmonic scissors; (F) dissection of the anterior part of the right lobe; and (G and H) the releasing of the last posterior adhesions with the help of the superior adenoma lifting.

facilitate better vision (**Figure 3A**). In extremely large prostates, it may be required to resect the median lobe priorly. The anterior plane is then approached and followed caudally. The extent of the resection begins proximally from the bladder neck, distally to the verumontanum. Care must be given not to injure the urethra and the sphincter (**Figure 3B**). The adenoma is enucleated and placed into a specimen bag (**Figure 3C**). If the adenoma is extremely large, it may be cut into small pieces by endoscissors and put in the specimen bag to secure.

Once the adenoma is enucleated, the pneumoperitoneum provides better visualization of arterial capsular bleeders that can be controlled with harmonic scissors. If bladder neck bleedings originate from the intravesical pedicle, ligation with V-loc hemostatic sutures or placement of M-knots with a 3-0 Vicryl can be used. Trigonization is described as plication of the bladder neck over the posterior capsule and performed in an interrupted fashion with 2-0 monocryl sutures (**Figure 3D** and **E**). The aim of this technique is to ensure the passage of the Foley catheter from the urethra into the bladder. Urethrovesical anastomosis has been proposed to ensure apposition of the bladder neck to urethral mucosa while helping the hemostasis and allegedly decreasing bladder neck contracture rates [21].

At the end of the hemostasis and trigonization, 22-F Foley catheter is replaced to the bladder, and cystostomy is closed with 2-0 Vicryl with interrupted sutures (van Velthoven technique) (**Figure 3F** and **G**) [22]. After closing the cystectomy, the balloon is filled with 30-ml saline, and urinary leakage is controlled by filling the bladder (**Figure 3H**). A Jackson Pratt drain is replaced to the Retzius space. Specimen is taken out from the port below the umbilicus.

#### *2.2.2. Laparoscopic transcapsular (Millin) technique*

The retropubic approach can be done utilizing several incisions. Transverse anterior prostatic, longitudinal anterior prostatic incisions and longitudinal prostatovesical and transverse incision just proximal to the prostatovesical junction are some of the choices. Sotelo et al. described their technique as they use the transverse incision adjacent to the prostatovesical junction. This technique avoids bleeding of the venous plexus. The other recommendation of Sotelo et al. is resection of the adenoma as separate lobes for improved visualization [21]. The use of suprapubic hand port is another modified technique. The hand port usage improves the speed of resection and provides hemostatic control [22].

The superiority of the transvesical technique over transcapsular (Millin) technique is identifying the intravesical median lob and allowing the dissection without injuring the orifices.

Regardless of the type of dissection chosen, the bladder irrigation for 24 h and urethral catheterization for 3–4 days are adequate postoperatively.

### 2.3. Complications

A complete cardiovascular workup should be performed during patient selection and surgical planning. Major complications are incontinence, bleeding, and cardiac complications. They account for much of the morbidity and mortality.

Patients should be screened for prostate cancer before undergoing surgery. The incidental prostate cancer rates may increase up to 10% of specimens in larger series [16, 23–30].

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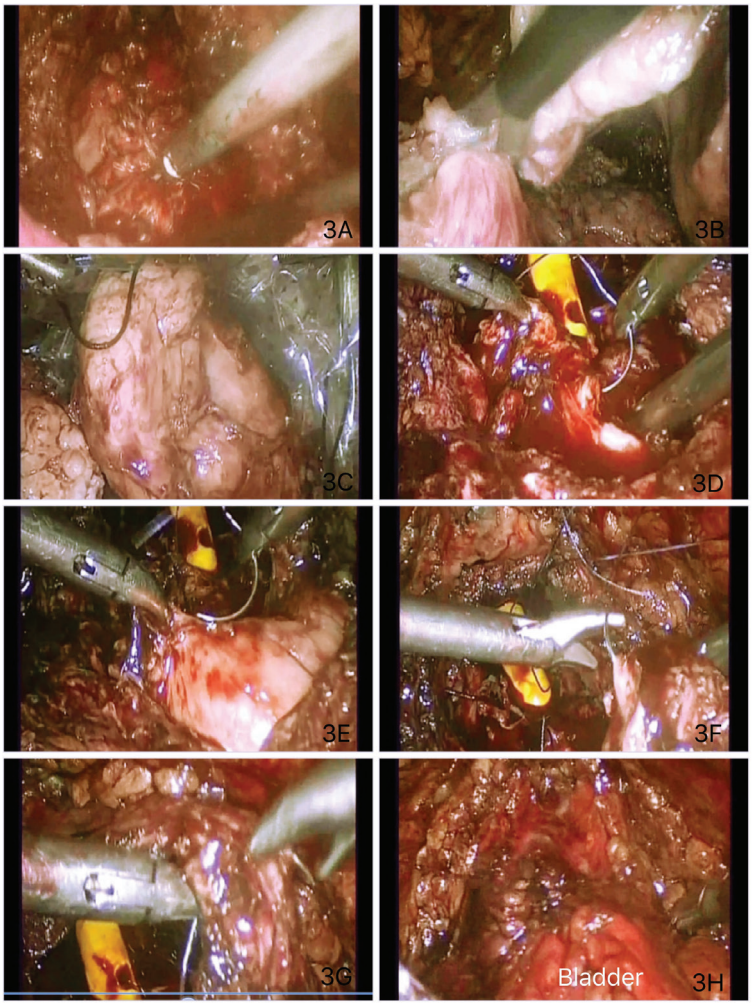


**Figure 3.** (A) The residual bleedings at the fossa are controlled by harmonic scissors; (B) the last adhesions are separated by endoscissors; (C) the adenoma is placed in the endobag; (D) the bleedings at the fossa are controlled with 3/0 Vicryl or V-loc hemostatic sutures; (E) trigonization is performed with plication of the bladder neck over the posterior capsule and facilitated in an interrupted fashion with 2-0 monocryl; (F and G) after 22-F Foley catheter is replaced to the bladder, cystostomy is closed with 2/0 Vicryl interrupted sutures; and (H) the bladder is finally filled with 200-ml saline in order to see if there is any leakage.

## 3. Discussion

Schuessler performed first laparoscopic radical prostatectomy in 1991 [31]. In 2002 Mariano et al. and in 2005 Sotelo et al. also performed laparoscopic simple prostatectomy for BPH [20, 21]. Mariano et al. reported first results of laparoscopic prostatectomy in 60 BPH patients with mean prostate weight of 144.50 ± 41.74 g. The mean operation time was 138.48 ± 23.38 min

with blood loss of 330.98 ± 149.52 mL and without any postoperative urinary incontinence [20]. Sotelo and van Velthoven et al., with minor modifications with the surgical technique, reported similar successful results without postoperative complications [21, 22].

Although initial results are encouraging, and its benefits including less blood loss and shorter hospital stay are better than the open surgery, there are very limited studies in the literature comparing the results of LSP with open prostatectomy [23, 32–34]. Most studies report the results of the small case series of LSP with different surgical approaches such as extraperitoneal, transperitoneal, transcapsular, or finger-assisted approaches [19–22, 31, 35–37]. In the literature, the results of extraperitoneal or transperitoneal techniques are reported to be similar without any superiority to the other [16–18].

Hoepffner et al., in their study with the biggest series published, reported 100 patients' results with mean prostate weight of 97.1 ± 18.5 g, mean operation time 66.3 ± 12.3 min with blood loss of 250 ± 86.8 ml without the need of blood transfusion with mean hospital stay of 4.2 ± 1.3 days and mean catheterization time of 3.2 ± 1 days [38]. Oktay et al. reported the results of 16 LSP patients with the biggest prostate weight, 147 g (between 80 and 200 g), mean operation time 133 min (75–210 min), mean blood loss 134 ml (50–300 ml) requiring one transfusion, hospital stay 3.9 days (2–7 days), and catheterization duration of 6.3 (6–7) days [39].

Chlosta et al.., in their series of 66 patients, reported surgery time of 55 (45–85) minutes as the shortest surgery time and similar results for blood loss, hospital stay, and catheterization time [40].

There are four studies comparing the results of LSP with open prostatectomy. Three studies with small number of patients reported less blood loss [23, 32, 33], less hospitalization time [17, 18, 20], and less catheterization time [32–34]. One study with bigger number of patients, by McCullough et al., compared the results of 96 LSP patients with 184 open prostatectomy patients and found no statistically significant difference in blood loss (350 vs. 400 ml) and in prostate volume (111.3 vs. 117.2 g) between two techniques; however, statistically significant differences were found in terms of hospitalization time (6.3 vs. 7.7 days) ($p < 0.001$) and catheterization time (5.2 vs. 6.4 days) ($p < 0.001$) [34].

Porpiglia et al. reported statistically significant difference in blood loss between two techniques. Although the operation time, hospitalization, and catheterization time were longer in LSP than in the open prostatectomy, no significant differences are reported [23].

## 4. Conclusion

Simple prostatectomy although is still the treatment of choice in larger prostates and may be performed effectively via several techniques, newer technologies offer minimally invasive techniques for both patients and surgeons. If patients are able to reach or purchase, the outcomes may increasingly be better. It is obvious that LSP has as steep learning curve comparable to open prostatectomy but is a minimally invasive surgery and has satisfying results in larger prostates with low morbidity and hospital stay in the hand of experienced surgeons. Our goal is the final outcome of improved LUTS and decreasing residual volume while minimizing the cost and the complications.

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## Conflict of interest

No conflict of interest.

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Chapter 6

# Endoscopic Extraperitoneal Transvesicocapsular Adenomectomy of Prostate (EETAP): A New Operative Method with an Innovative Learning Protocol for Its Performance

Genadiev Tsvetin Trifonov

**Abstract**

The standard surgical treatment of obstructive symptoms of the lower urinary tract by benign prostatic hyperplasia is transurethral resection or classical simple prostatectomy. Inspired by our experience with laparoscopic radical prostatectomy and for the protection of urethra from stricture during prolonged transurethral resection, we studied the literature and started a prospective study for performing a laparoscopic simple prostatectomy. Following informed patient consent, we performed laparoscopic extraperitoneal simple prostatectomy in 17 patients with moderate to severe obstructive symptoms of benign prostatic hyperplasia with a prostate volume of over 80 ml. We did not find a laparoscopic technique for a simple prostatectomy which is the same as our method that we describe and publish. We called our method endoscopic extraperitoneal transvesicocapsular adenomectomy of prostate. We identified an abbreviation for the method of its popularization and systematic presentation, EETAP. In this chapter, we publish for the first time in the literature a minimally invasive surgical method for endoscopic extraperitoneal transvesicocapsular prostate adenomectomy. We describe and publish the details of the method, the abbreviation of the method, an innovative learning protocol for its performance, as well as hypotheses for preoperative and intraoperative differential diagnosis. In our opinion, a multicenter study of this method could lead to its standardization in the broad urological practice.

**Keywords:** new minimal invasive operative method, simple prostatectomy, endoscopic extraperitoneal transvesicocapsular adenomectomy, prostate, EETAP, obstructive symptoms of the lower urinary tract, benign prostatic hyperplasia, laparoscopic extraperitoneal simple prostatectomy, innovative learning protocol, preoperative and intraoperative differential diagnosis, urine genetic test, new urine prostate cancer test indications

## 1. Introduction

For operative treatment of benign prostatic hyperplasia, transurethral resection is used as a standard for prostatic volume up to 75 ml. For larger volumes of the prostate, there is a classic open simple prostatectomy, which we call adenomectomy. The laparoscopic surgical technique was introduced into urology in 1991 with the publication of Schuessler et al. for pelvic lymph node dissection for prostate cancer staging [1]. Shortly thereafter, the first laparoscopic radical prostatectomy published by the same author was performed [2]. The first laparoscopic simple prostatectomy was performed in 1999 by Mariano Mirandolino [3]. In the last 10 years, the laparoscopic surgical technique has been used for the operative treatment of benign prostatic hyperplasia. Various minimally invasive methods for simple prostatectomy performed by laparoscopy are found in the literature. Laparoscopy is performed by transperitoneal access, classical laparoscopy, and extraperitoneal access—endoscopic extraperitoneal technique. A greater number of methods are not described in detail and consistently. Encouraged by our experience with laparoscopic radical prostatectomy and for the protection of the urethra from stricture during prolonged transurethral resection, we started a prospective study to perform and validate endoscopic extraperitoneal surgery for simple prostatectomy in benign prostatic hyperplasia, BPH. We have defined and described the main points of the surgical technique of simple prostatectomy. We present a detailed step-by-step approach to our method. In order to use the experience of a similar laparoscopic method, we compared all the steps of the new method with the previously described surgical technique for endoscopic extraperitoneal radical prostatectomy. We created an innovative protocol for learning and performing the new method based on a comparison of the two surgical methods performed in prostate cancer and prostate adenoma. From this protocol, we built a hypothesis for a new intraoperative approach to suspected carcinoma by express histological examination of the enucleated adenomatous tissue and an assessment of the volume of surgery—radical prostatectomy or adenomectomy. This hypothesis is to be explored. We have also developed a second hypothesis for preoperative differential diagnosis of aggressive prostate cancer by a noninvasive urine test SelectMDx/MDxHealth, Irvine, CA, USA, and Europe, to avoid classical biopsy in selected patients. The role of this hypothesis is related to the presence of 10% incidental cancer in patients after simple prostatectomy, and some authors perform a preoperative classical prostate biopsy on all patients. The indications for urine test performance are limited by the use of 5-alpha-reductase inhibitors as well as in patients with permanent urethral catheter due to inability to spontaneously urinate. However, the method could be used in patients who are candidates for a simple prostatectomy in order to prevent a second operation for incidental prostate cancer. Until now, such indications have not been determined for this urine test.

## 2. Materials and methods

### 2.1. Patients

For the period 2014–2017, 17 men, n = 17, of average age 64 years, from 48 to 76, were operated in the Urology Department of Vita Hospital, Sofia, and in the Urology Clinic of Uni

Hospital, City of Panagiurishte. In all, endoscopic extraperitoneal transvesicocapsular adenomectomy of the prostate (EETAP) was done. Preoperative prostate diagnosis was made by PSA total and free, rectal digital prostate examination, transrectal ultrasound, abdominal ultrasound, and flexible urethrocystoscopy. The mean volume of prostate adenoma measured by transrectal ultrasound was 95 ml, 75–140. We performed an evaluation of the international prostate symptom score preoperatively only in patients without residual urine. We have used uroflowmetry in patients with early symptoms of prostate obstruction. Four patients underwent transrectal tru-cut ultrasound prostate biopsy before adenomectomy. We did not have a patient with transurethral resection of the prostate before surgery. All patients signed informed consent for the proposed operation and probability of occlusive prostate cancer despite negative preoperative diagnosis and biopsy. The surgical team has experience in prostate cancer diagnosis and laparoscopic radical prostatectomy. All operations were performed by a single major operator, TTG. This operator is a laparoscopic urologist with experience in endoscopic extraperitoneal radical prostatectomy, experienced in transvesical open simple prostatectomy, but not experienced in open transcapsular Millin adenomectomy.

### 2.2. Indications

Patients with benign prostatic hyperplasia (BPH), prostate adenoma, and symptoms of obstruction of the lower urinary tract. Prostate volume over 75 ml measured by transrectal ultrasound.

### 2.3. Contraindications

General contraindications for laparoscopic method—impaired pulmonary and cardiovascular status—as well as those with impaired blood clotting. Patients with a history of a brain accident in the past have been consulting a neurologist to determine the risk of surgery related to Trendelenburg position. Patients with prior inguinal hernioplasty, with or without mesh plastic, have not been contraindicated. Patients with bladder stones or a large prostatic middle lobe are not contraindicated for our method. Asymptomatic uroinfection is not a contraindication to surgery. We do not have pre-treatment and apply a triple antibiotic combination at the beginning of the operation.

## 3. Operative technique EETAP

In EETAP, preoperative patient preparation, anesthesia, patient's operating table position, operating team position, equipment location in the operating room, type of apparatus and instruments, and position and type of trocars completely coincide with those of endoscopic extraperitoneal radical prostatectomy, EERPE [**Table 1**]. An additional tool is the laparoscopic morcellation device with its own trocar 10 or 12 mm.

### 3.1. Preoperative patient preparation

Diet regimen, the day before the operation, is as follows: normal daily meals and liquid supper at 18o'clock. Preoperative laxative preparation with suppositories for rectal administration.

| | Author/year of publication | Patients, n = | Title name of the method and his abbreviation, if there is, according to the author's publication | Pelvic operative access—trans- or extraperitoneal | Access to adenoma via bladder wall incision, prostatic capsule incision, or vesicocapsular incision | Method of extraction the adenoma from the patient endobag or morcellation |
|---|---|---|---|---|---|---|
| 1 | Mariano et al., 2002 [3] | 1 | Laparoscopic prostatectomy with vascular control for benign prostatic hyperplasia | Trans | Midline bladder and capsular incision | Morcellation |
| 2 | Nadler et al., 2004 [19] | 1 | Preperitoneal laparoscopic simple prostatectomy | Extra | Transversal capsular incision | Endobag umbilical extraction |
| 3 | van Velthoven et al., 2004 [20] | 18 | Laparoscopic extraperitoneal adenomectomy (Millin) | Extra | Transversal anterior incision of the prostate capsule | Is not explained |
| 4 | Rey et al., 2005 [21] | 5 | Laparoscopic adenectomy: a novel technique for managing benign prostatic hyperplasia | Extra pre-peritoneal space by a Veress needle | Prostatic capsule is opened 3–4 cm transversally | Laparoscopic bag extracted through the enlarged umbilical incision |
| 5 | Sotelo et al., 2005 [22] | 17 | Laparoscopic simple retropubic prostatectomy | Extra | Transverse cystotomy | Endobag |
| 6 | Rehman et al., 2005 [23] | 20 | Laparoscopic extraperitoneal adenomectomy (LEA) | More than 20 | Transversal capsulotomy | Endobag morcellated removed through the subumbilical incision |
| 7 | Mariano et al., 2006 [24] | 60 | Laparoscopic prostatectomy for benign prostatic hyperplasia, a 6-year experience | Extra | Midline incision anterior aspect of the prostatic capsule and bladder neck | Morcellation |
| 8 | Porpiglia et al., 2006 [25] | 20 | Transcapsular adenomectomy (Millin): a comparative study, extraperitoneal laparoscopy versus open surgery | Extra | Transversal capsular incision | Endobag through umbilical port |
| 9 | Oktay et al., 2011 [26] | 16 | Laparoscopic extraperitoneal simple prostatectomy for benign prostate hyperplasia | Extra | Transverse incision at the vesicoprostatic junction of the bladder | Is not explained |

| | Author/year of publication | Patients, n = | Title name of the method and his abbreviation, if there is, according to the author's publication | Pelvic operative access—trans- or extraperitoneal | Access to adenoma via bladder wall incision, prostatic capsule incision, or vesicocapsular incision | Method of extraction the adenoma from the patient endobag or morcellation |
|---|---|---|---|---|---|---|
| 10 | Ramón de Fata Chillón et al., 2010 [27] | 10 | Laparoscopic extraperitoneal adenomectomy | Extra | Vertical capsulotomy from the prostatic apex up to 1 cm above the bladder neck | Laparoscopic bag through the enlarged umbilical incision |
| 11 | Yun et al., 2010 [28] | 11 | Laparoscopic retropubic simple prostatectomy | Extra | Transverse incision of the anterior prostatic capsule | Endobag sac |
| 12 | García-Segui and Gascón-Mir, 2012 [29] | 28 | Laparoscopic extraperitoneal adenomectomy (LEA) | Extra | Transverse incision is made at the vesicoprostatic junction | Endobag sac |
| 13 | Xing et al., 2010 [30] | 51 | Laparoscopic simple prostatectomy with prostatic urethra preservation | Extra | Transverse prostatic capsular incision | Endobag |
| 14 | Pedro Romanelli de Castro et al., 2013 [31] | 15 | Laparoscopic retropubic prostatectomy: initial experience | Ten trans<br>Five extra<br>peritoneal | Opening of the prostate capsule and the bladder neck was made by longitudinal incision | Bagged and removed after morcellation through the umbilical incision |
| 15 | Al-Aown, 2015 [32] | 11 | Laparoscopic simple rostatectomy (LSP) | Extra | 3–4 cm vertical cystotomy incision | Endobag |
| 16 | Autorino et al., 2015 [18] | 843 | Minimal invasive simple prostatectomy (MISP) | Extra | Is not explained | Is not explained |
| 17 | Garcia-Segu et al., 2015 [33] | 26 | "Knotless" laparoscopic adenomectomy | Extra | Is not explained | Morcellated adenoma extracted through the umbilical incision |
| 18 | Nicoline et al. 2016 [34] | 17 | Endoscopic transvesical adenomectomy of the prostate (ETAP) | Extraperitoneal but trans vesical percutaneous access | Intravesical bladder incision | Endobag/extraction bag/no data on how exactly to do this |

| | Author/year of publication | Patients, n = | Title name of the method and his abbreviation, if there is, according to the author's publication | Pelvic operative access—trans- or extraperitoneal | Access to adenoma via bladder wall incision, prostatic capsule incision, or vesicocapsular incision | Method of extraction the adenoma from the patient endobag or morcellation |
|---|---|---|---|---|---|---|
| 19 | Biktimirov et al., 2017 [35] | 79 | Minimal invasive simple prostatectomy MISP | Extra | Transverse incision of the anterior prostatic capsule | Removed through the 10 mm port site beneath the umbilicus |
| 20 | Baldini et al., 2017 [36] | 28 | Laparoscopic transcapsular prostatectomy (LTP) | Transperitoneal | Transverse prostatic capsular incision | Is not explained |
| 21 | Genadiev TS, 2018 [12] | 17 | Endoscopic extraperitoneal transvesicocapsular adenomectomy of the prostate (EETAP) | Extra | Transvesicocapsular incision | Morcelation and fragment extraction through the trocar or not morcelated in bag extraction through the left lateral trocar |

Extra = extraperitoneal access. Trans = transperitoneal access. Is not explained = there is no explanation of the method in the text.

**Table 1.** The cited authors on the topic with their main points of the surgical method.

Scheme of administration is as follows: the evening before the surgery at 8 o'clock a suppository and in the morning at 6o'clock before surgery the second suppository. In patients with delayed intestinal passage, we prescribe the oral laxative tablets the day before the operation. Exceptionally, with an unsatisfactory laxative effect, we perform rectal cleansing enema in the morning before the operation. The field of operation is hairless in the evening before the day of surgery. All patients enter the operating room with elastic socks on the legs up to the middle of the thigh. Patients with permanent urethral catheter and urinary tract infections enter the operating room without a catheter. At the beginning of the operation, a combination of antibiotics—cephalosporin, aminoglycoside, and metronidazole—is administered intravenously. In the postoperative period, cephalosporin continues until the patient's discharge, usually 3 days. According to our protocol, prophylaxis with low molecular heparin begins at the sixth hour after the end of the operation. In patients with cardiovascular risk or postoperative bleeding, prophylaxis occurs outside of this protocol.

### 3.2. Anesthesia

All patients were operated under intubation endotracheal anesthesia with a peripheral venous pathway. Nasogastric tube is not required due to low pressure in the peritoneal cavity in extraperitoneal access. In order to provide free space for the cameramen behind the patient's head, it is necessary to use extended infusion and inhalation systems that distance the anesthesia team and the inhalation device from the patient. A preoperative discussion of the operating time is performed due to the faster onset of hypercapnia in the patient, which is typical for extraperitoneal laparoscopic access. This can be offset by the use of an insufflator with controlled maintenance of the working pressure and dosing of the carbon dioxide flow.

### 3.3. Position of the patient and operating team

The operating table should have a height of less than 60 cm from the floor level to achieve a good patient operating position and team ergonomics. The patient on the operating table is in the supine position. The hands are fixed to the body. To prevent compartment syndrome and for good blood circulation, the patient's legs remain on the horizontal pads of the operating table without the use of footwell attachments. Also the patient's legs are at the chest level during the Trendelenburg position. The legs remain dissolved at about 30° for access to the rectum, if necessary. At the patient's chest level, a moderately tight belt, 15 cm wide, with a soft pad, is provided to secure the 15° Trendelenburg position—**Figure 1**. Attention is needed against strong chest tightness and difficulty in breathing, as well as against mammary gland trauma.

Location of the operating team—the operator is to the left of the patient, assistant first to the right of the patient, second assistant, and cameramen, behind the patient's head. Surgical nurse is in front of assistant first, to the right of the patient, **Figure 2**.

### 3.4. Equipment and instruments

Olympus laparoscopic set with automatic insufflator. High-frequency bipolar current generator and ultrasound—Thunderbeat, manufactured by Olympus, Germany, **Figure 3**. Laparoscopic

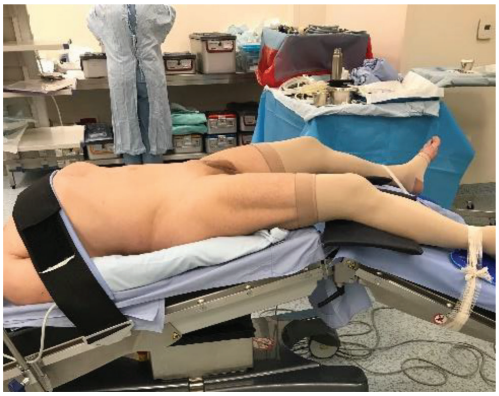

**Figure 1.** Patient's position on the operative table.

instruments manufactured by Olympus, reusable trocars 5 and 10 mm, Hasson conical trocar 10 mm, and Thunderbeat laparoscopic instrument handle 5 mm, with combined action ultrasonic scissors and bipolar coagulation. Bipolar and traction forceps, needle holders, 5 mm cannula for aspiration, and irrigation with buttons and with piston handle. We do not use any cold scissors during the operation. Stitches are cut with Thunderbeat instrument. The Laparoscope 10 mm with detachable camera head, 0°. Working pressure of carbon dioxide is 12–14 mm mercury. Laparoscopic morcellator devise with 10 mm trocar and grasping forceps 10 mm, manufactured by Richard Wolf, Germany. Morcellation operating speed is 1000 rpm.

The key instruments are Thunderbeat instrument, bipolar forceps, and suction/irrigation 5 mm cannula with pistol handle with two buttons, **Figure 4**.

### 3.5. Operative access to the pelvis

Operative pelvis access is an endoscopic extraperitoneal balloon dissection of the Retzius space. Performing the pelvic operative field and trocars placement is carried out in a horizontal

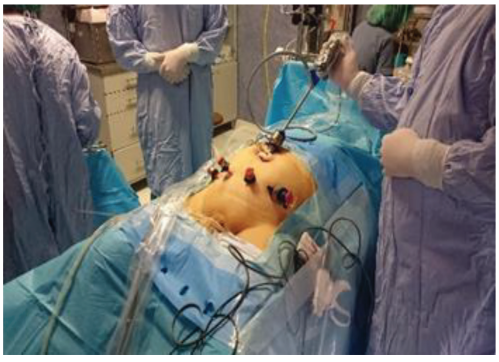

**Figure 2.** Position of the operating team.

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**Figure 3.** Olympus laparoscopic set with automatic insufflator with high-frequency bipolar current generator with ultrasound source, Thunderbeat, manufactured by Olympus, Germany.

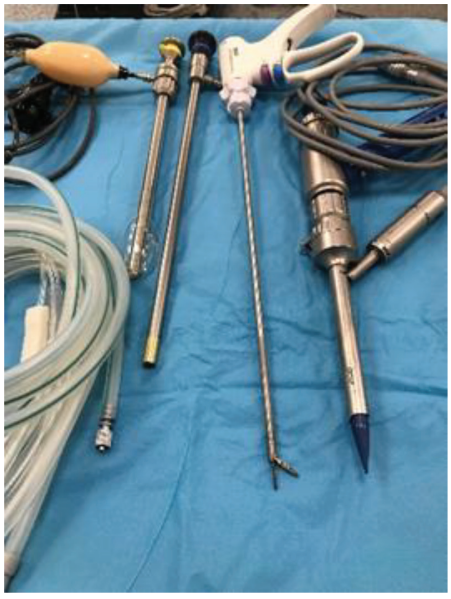

**Figure 4.** Key instruments: laparoscopic morcellator devise with 10 mm trocar, manufactured by Richard wolf, Germany. Thunderbeat instrument 5 mm, Herloon system for extraperitoneal access.

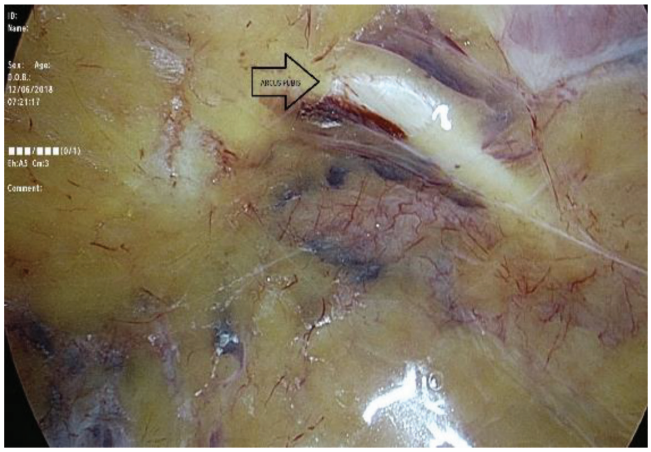


**Figure 5.** Internal pelvic view through balloon dissector with 10 mm laparoscope shown arcus pubis.

position of the patient to prevent the unnecessary Trendelenburg position. We use balloon dissection device manufactured by Covidien/OMSPDB1000 PDP Round Distension Balloon disposable balloon disposer or by B. Brown or the Herloon System for extraperitoneal access, B. Braun, Aesculap AG, Tuttlingen, Germany. Laparoscopic morcellator devise with 10 mm trocar and grasping forceps 10 mm, manufactured by Richard Wolf, Germany. Approximately 2 cm below the navel is a horizontal 2 cm incision of the skin. The incision site is determined by the depth and width of the pelvis of the patient to ensure good distance of the optic trocar to operative field and against collision with the other trocars. If the patient has a narrow pelvis, then the skin incision can be made slightly to the right of the assistant's side to ensure a good distance between the trocars of the operator. After the skin incision, the fascia of the anterior

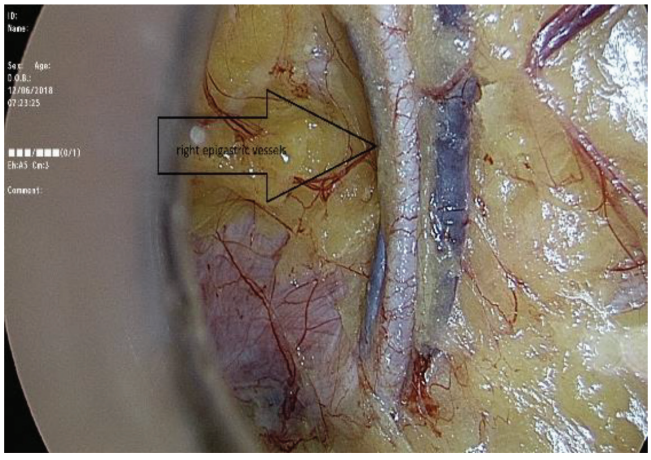


**Figure 6.** Internal pelvic view through balloon dissector with 10 mm laparoscope shown epigastric vessels.

abdominal wall is reached, which is the anterior fascia of the right abdominal muscles. It is incised transversely about 1–2 cm. Under the fascia, the right abdominal muscles are separated until the peritoneum is detected. Between the peritoneum and the anterior abdominal wall, with the help of the index finger on the right arm, enough space is created for the balloon dissector. The balloon is pumped under visual optical control until the appearance of the pubic arc and the internal epigastric vessels on both sides, **Figures 5** and **6**. After removing the balloon, a Hasson conical trocar is placed and fixed to the abdominal fascia with two slowly absorbable 2/0 Vicryl sutures with "j"-shaped needle, which are finally used to close the fascial insertion. In the case of adhesions of the anterior abdominal wall, which the balloon dissector cannot overcome, the trocars on the opposite side are placed. Adhesion dissection is performed, and access for other trocars is made.

### 3.6. Trocars: number, type, sequence of placement, and position

The trocars are five. Just the Hasson optical trocar has a smooth surface, because the cone allows to adjust the trocar penetration. Other working trocars must have a spiral surface or accessory fixators to adjust their depth due to the small operative field in the pelvis. Order of placement is as follows: 10 mm cone trocar for laparoscope with adjustable and fixed depth, left side lateral trocar 10 mm with 5 mm reducer, followed by left medial 5 mm, right lateral 5 mm, and right medial 5 mm. Trocars' position is as follows: the two lateral trocars are placed about 2 cm medial from the spina iliaca anterior superior, **Figure 7**. The two medial trocars are placed about 4–5 cm from the lateral ones at a position that provides about 45° of angle between the two working instruments, especially important for inner suturing. These trocars should be placed more cranially for easier suturing of the bladder wall.

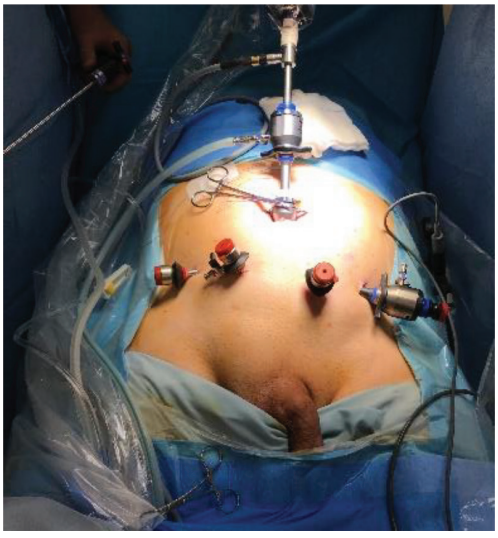

**Figure 7.** Trocar's position.

## 4. Operative technique of the inner part of the EETAP

### 4.1. Incision of the prostatic capsule and bladder neck: transvesicocapsular access to prostate adenoma

Fatty tissue and blood vessels of plexus Santorini are dissected to discovery just the middle surface of the prostatic capsule and the anterior surface of the bladder neck. No hemostatic ligatures on the bladder or capsule are required. The endopelvic fascia, the prostatic ligaments, and dorsal vein complex remain intact. The balloon catheter traction can be used to find bladder neck. The ultrasonic instrument Thunderbeat performs an incision of about 2 cm on the front wall of the bladder in the area of the bladder neck. Immediately after opening the bladder and finding the urethral catheter, the incision continues with the opening of the anterior surface of the bladder neck in the direction of the prostate capsule. Longitudinal incision of the prostatic capsule extends beyond the level of the puboprostatic ligaments to allow good apical dissection and urethral cutting. This is a key point in the EETAP operation and is called transvesicapsular incision, **Figures 8** and **9**.

The advantages of this method are as follows: provides bladder access and inner examination, access to prostate adenoma, good plan for enucleation even in large median lobe, accessibility and good visibility for dissection of the apical part of the urethra without extreme traction of adenoma, good possibilities for bladder trigonisation, large postoperative bladder neck and possibility to avoid trigonisation; spares the inner pelvic anatomy such as dorsal vein complex, puboprostatic ligaments, the prostatovesical pedicles, and the endopelvic fascia to allow conversion to radical prostatectomy if necessary; and allows the same trocars position as EERPE in case of conversion. This method allows good large enucleation plan with prostate capsule preservation from rupturing in the lateral direction where the vascular bundles are located, which is important for our hypothesis of switching to radical prostatectomy during surgery. Last but not least, the transvesicocapsular incision is intuitive to perform and recover for a right-handed surgeon without changing the trocars during inner suturing.

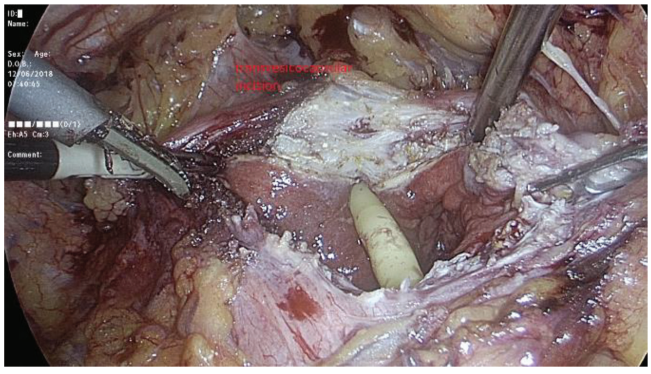


**Figure 8.** Transvesicocapsular incision—*before* adenoma enucleation. The bladder neck is incised at 12o'clock position longitudinally close to prostatic ligaments. The incision is in deep to the adenoma.

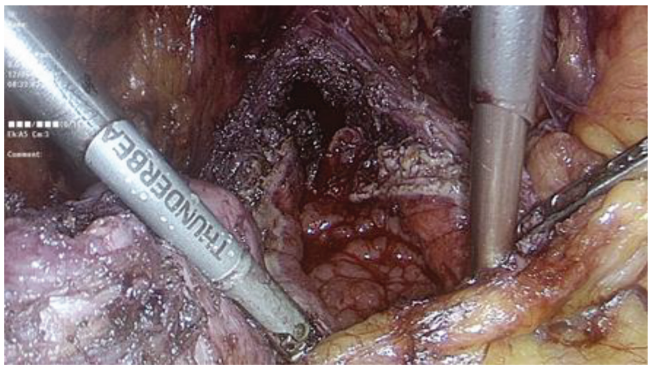


**Figure 9.** Transvesicocapsular incision—after adenoma enucleation. The prostatic bed is empty. Adenoma is on the left side of the picture.

### 4.2. Enucleation of adenoma

The enucleation of the adenoma begins with the finding of a plan between the prostate capsule and the adenomatous tissue. This is most often done from the front surface of the bladder neck that is already open to the incision. So if there is a middle prostatic lobe, it does not make it difficult to find a plan. Moreover, if the middle lobe is large, a good plan can be found between its mucosa and the adenoma starting from 6o'clock position of the bladder neck. The enucleation of adenoma is performed by Thunderbeat/Olympus combined with ultrasonic scissors and bipolar coagulation forceps and second bipolar forceps, **Figure 10**. Thus, the bipolar coagulation is possible on the two hands of the operator. With these two instruments, all enucleation is performed without the need for hemostatic ligatures of the internal prostatic pedicles that are coagulated with bipolar forceps. Enucleation is performed under visual control and in a visible manner between the capsule and the adenomatous tissue, following a good and possible plan. If the plan is lost, it goes into another plan. In the case of difficulties in the volume

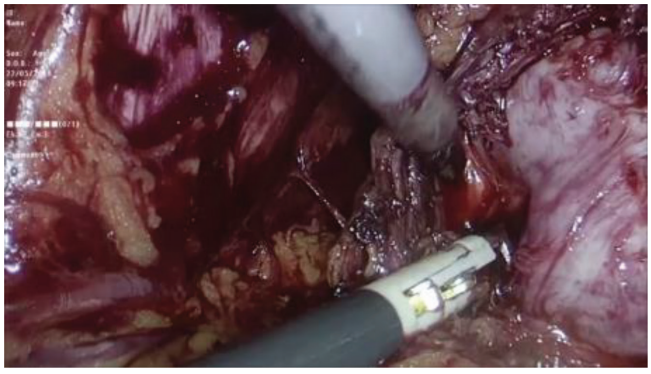

**Figure 10.** Enucleation plan between capsule and adenoma of the prostate via bipolar forceps and Thunderbeat instrument.

of adenoma, it goes to its division and enucleation of parts. Apical dissection of the urethra requires attention. In this method, this is done with mild or without any traction, and a visible plan to find urethra and colliculus seminalis is to ensure good postoperative urine continence.

### 4.3. Removing adenoma out of the patient

In our method, removal of the adenoma from the patient is done in two ways. The first method is as follows: a left lateral trocar is extracted and replaced with the laparoscopic morcellator with his own trocar without expanding the trocar hole. The adenoma is morcellating over the prostatic capsule with extraction of the each fragment via grasper immediately after his own morcellation. Beware of residual fragments in the bladder and on the pelvic wall! At the end of the morcellation, a revision of residual fragments is performed. The morcellator is pulled out under optics control, and the working trocar is reinserted, **Figure 11**.

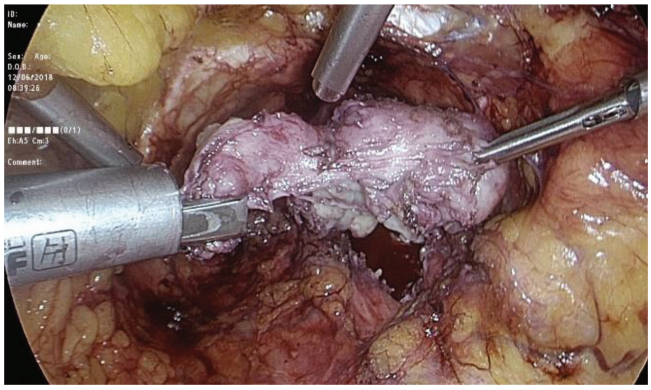


**Figure 11.** Morcellation of the adenoma. The morsellator is placed through the left lateral trocar hole without skin extension.

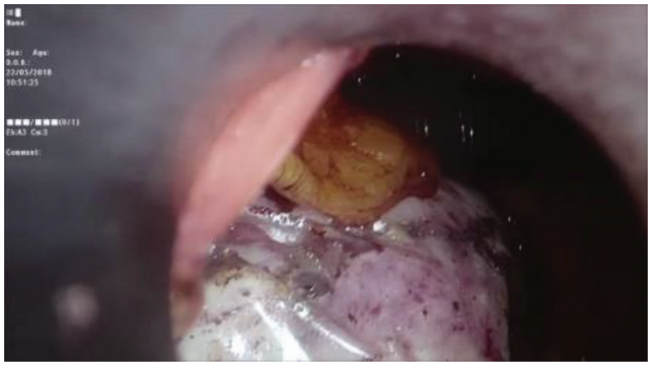


**Figure 12.** Enucleated adenoma in endobag and fixed through the left lateral trocar hole. The endobag can be extracted for histology examination.

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The second method is as follows: after complete release of the adenoma, it is placed in an endobag/sterile laparoscopic plastic bag that is fixed around the left lateral trocar and remains thus until the end of the inner part of the operation, **Figure 12**. This method is the same as in EERPE technique and allows extracting adenoma for an express histology test for cancer during the operation. If not necessary, then at the end of the operation, the left lateral trocar is removed, and his opening widens, and the endobag is removed through it. In order not to extend the trocar hole too far, the adenoma is subdivided by ultrasonic scissors into smaller fragments within the endobag. The removed material is fixed in formalin for a histological preparation.

### 4.4. Closure of the transvesicocapsular incision

Prostatic bed hemostasis is performed with bipolar coagulation at reduced working pressure of carbon dioxide up to 8 mm mercury. After hemostasis of the prostatic bed, 3-0/Monocryl™ Plus, MCP 4160, Ethicon®, needle 1/2c, 26 mm, and Johnson and Johnson; hemostatic sutures of the bladder neck on the 5 and 7o'clock position are made, and suturing the trigonum as close as possible to the urethra is performed. This is the so-called trigonisation, **Figure 13**. Following trigonisation, a three-way 22 charier catheter is inserted in the urethra to the bladder. The incision of the prostate and bladder wall is restored with continuous suture 2-0 monocryl/Vicryl™, Ethicon®, Johnson and Johnson, W9121, 26 mm, 1/2c needle, **Figure 14**. The suture starts from the apical part of the prostatic capsule and continues to the bladder wall up to the end of incision. Care should be taken not to suture the catheter. At the end of suturing, the catheter is checked for mobility. Then the balloon is placed sure in the bladder and inflated with 60 ml saline. Verification of the bladder for leakage, and start the irrigation through the catheter. Place a 14–16 charier tube drainage through a right lateral trocar hole. The skin of the trocar holes is closed with tissue glue/Hystoacryl® 0.5 ml, B. Braun Surgical, S.A./except for the hole in the tube drain. In this method the bladder neck inside remains open, with the suture engaging only the front of the bladder wall. Thus, we believe that a broad bladder-to-prostate communication is created to prevent post-operative bladder neck

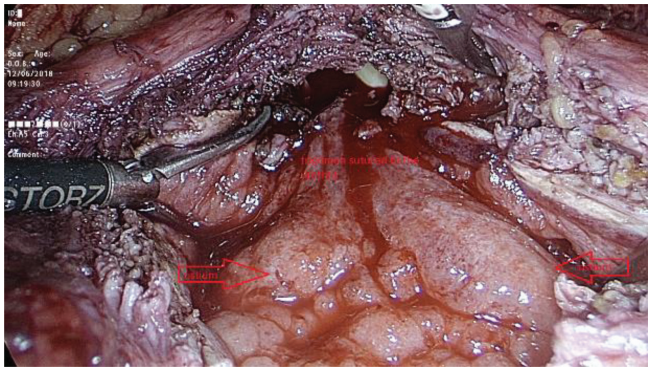


**Figure 13.** Bladder trigonisation. The wide bladder neck remains open after incision closure.

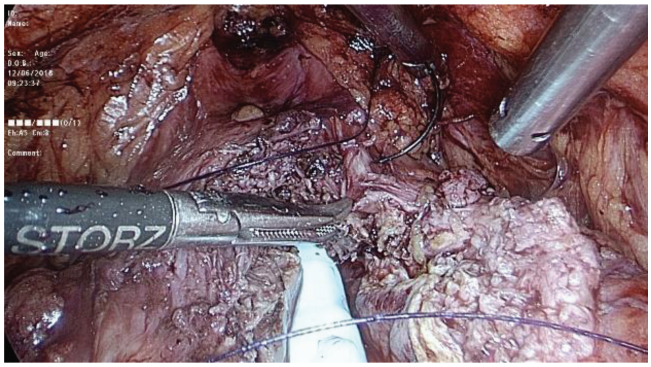


**Figure 14.** Closure of the transvesicocapsular incision with 2/0 Monocryl continuous suture over the urethral catheter.

sclerosis. Furthermore, this extensive communication does not make trigonisation mandatory if there are technical difficulties to do so.

### 4.5. Postoperative protocol

Our postoperative recovery protocol for EETAP is the same as our EERPE protocol. The only difference is the catheter irrigation after adenomectomy. This recovery protocol has the following steps: 6 hours after anesthesia, the patient is under monitoring, moves up, and takes fluids at the end of the sixth hour after the end of anesthesia. Thirty minutes before the movement, a subcutaneous application of low molecular heparin was administered. The irrigation of the catheter is stopped the next day, which is the first postoperative day. The balloon of the catheter remains inflated till the cystography. On a second or third postoperative day, the patient leaves the clinic. Ambulatory therapy for a total of 10 days with antibiotic per oral and prophylaxis with low molecular heparin is used. After the sixth postoperative day, cystography is performed in the ambulatory, and the urethral catheter is removed. We monitor and interview the patient monthly for urinary infection and sclerosis of the bladder neck until the third postoperative month.

## 5. Results

Average operative time skin to skin was 150 minutes (from 90 to 180). Average catheter stay was 7 days/6–9 days. There was no case of blood transfusions. There was no case of operative conversion or postoperative open or laparoscopic revision. There was no case of major complication such as vessel thrombosis or postoperative death. There was one case of early postoperative transurethral revision due to hematuria but without prolonged catheter stay and blood transfusion. The our second patient, who had the 140 ml prostate,

mainly with big median lobe, required transurethral resection on the third month after EETAP due to the large prostatic residual tissue on both sides. In fact we had removal just the big middle lobe. One patient reports stress incontinence until 6 postoperative months. Without patients with new catheterization due to urinary retention. None of the patients reported impaired erectile function or full urine incontinence. There are five cases of subdermal hematomas, typical after extraperitoneal access. Preoperative prostate biopsy was performed in four patients. We did not have a case with accidentally exposed prostate cancer. All patients reported satisfaction with the first urination after catheter removal. From our postoperative observation and patient interview to 90 postoperative day, we did not have a patient with bladder neck sclerosis, bladder stones, or other urological postoperative complications.

## 6. Discussion

Our laparoscopic practice began in 2003 with our first laparoscopic staging lymph node dissection in prostate cancer [4]. In 2005 we introduced in our practice the Montsouris technique of transperitoneal radical prostatectomy [5, 6]. Three years later we start to perform the endoscopic extraperitoneal radical prostatectomy technique described by Stolzenburg et al., [7, 8]. We published a new endoscopic extraperitoneal method for bladder stones in 2011 [9]. In our diagnostic practice, we introduced the transrectal ultrasound tru-cut prostate biopsy in 2004 [10], the ratio of free to total PSA in 2005 [11], and urine test SelectMDx in 2017 [12]. These circumstances and the protection of the urethra from prolonged transurethral resection motivated us to carry out and validate the new EETAP method. For exploring and describing our method, we were guided by the main points of our technique—surgical access, access to the prostate capsule and adenoma, a method of removing adenoma from the patient. We only discuss sources and authors that are closely related to the keywords of our method. Authors describing laparoscopic robot-assisted, single-port, hybrid, and operative techniques other than our method are not discussed here.

According to the Guidelines of European Association of Urology, the term minimal invasive simple prostatectomy (MISP) includes laparoscopic simple prostatectomy (LSP) and robot-assisted simple prostatectomy (RASP) [13]. Both methods are based on the transcapsular (Millin) or transvesical (Freyer) techniques. According to Guidelines of American Urological Association, the methods with minimal invasion are called minimally invasive surgical therapies, MIST. There is no abbreviation for laparoscopic simple prostatectomy [14]. According to Canadian UA Guideline 2010 Update: Guidelines for the Management of Benign Prostatic Hyperplasia, minimally invasive surgical therapies (MIST), and in the open simple prostatectomy section, there is no word laparoscopy or other laparoscopic simple prostatectomies. No current data from the Canadian urologist association are available on this topic [15].

| Sequence of stages and their steps | Surgical technique step by step | EERPE<br>Prostate cancer<br>Stages and steps | EETAP<br>Prostate adenoma<br>Stages and steps | Match between EERPE and EETAP |
|---|---|---|---|---|
| **First stage in seven steps: preoperative and operative preparation** | | | | |
| 1 | Preoperative patient preparation | Yes | Yes | Match |
| 2 | Operating team | Yes | Yes | Match |
| 3 | Position of team in the operating room | Yes | Yes | Match |
| 4 | Patient table position | Yes | Yes | Match |
| 5 | Trendelenburg position | Yes | Yes | Match |
| 6 | Equipment | Yes | Yes | Match |
| 7 | Instrumental equipment | Yes | Yes | Match |
| **Second stage in four steps: operative access** | | | | |
| 8 | Pelvic endoscopic access via balloon dissection | Yes | Yes | Match |
| 9 | Trocars: numbers and kinds | Yes | Yes | Match |
| 10 | Trocar position | Yes | Yes | Match |
| 11 | Access to the prostatic surface | Yes | Yes | Match |
| **Stage three in seven steps: intracorporal part of both operative techniques** | | | | |
| 12 | Endopelvic fascia incision | Yes | No | Matchless |
| 13 | Ligation of the dorsal vessels of the penis | Yes | No | Matchless |
| 14 | Longitudinal transvesicocapsular incision of the prostate capsule and bladder neck | No | Yes | Matchless |
| 15 | Interruption of the bladder neck | Yes | No | Matchless |
| 16 | Enucleation of prostatic adenoma | No | Yes | Matchless |
| 17 | Prostatovesiculectomy | Yes | No | Matchless |
| 18 | Urethrovesical anastomosis | Yes | No | Matchless |
| **Stage four in five steps: final steps of the operations** | | | | |
| 19 | Removal of operative tissue via morcellation | No | Yes | Matchless |
| 20 | Lymph node dissection | Yes | No | Matchless |

| Sequence of stages and their steps | Surgical technique step by step | EERPE<br>Prostate cancer<br>Stages and steps | EETAP<br>Prostate adenoma<br>Stages and steps | Match between EERPE and EETAP |
|---|---|---|---|---|
| 21 | Removal tissue via endobag extraction | Yes | Yes | Match |
| 22 | Inner suture | Yes | Yes | Match |
| 23 | Kind of suture materials | Yes | Yes | Match |
| 24 | Trocars hole closure | Yes | Yes | Match |
| **Stage five in three steps: postoperative protocol** | | | | |
| 25 | Postoperative recovery period/ catheter irrigation mentioned | Yes | Yes | Match |
| 26 | Patient discharge on POD 3–4 | Yes | Yes | Match |
| 27 | Cystography on POD 5–7 | Yes | Yes | Match |
| Steps number, 27 | | **24/3** | **21/6** | |
| Steps matching/correlation ratio, yes/no | | | | |

Both techniques in this protocol are presented with the same full steps, 27, and the same stages, 5. EERPE and EETAP are comparable and matching them in almost complete. Endobag = laparoscopic plastic bag.

**Table 2.** This table presents the innovative learning protocol based on matching according to the main stages and the individual steps for each of the both operative techniques—EERPE and EETAP.

According to Tagard, transvesicocapsular adenomectomy was first described in 1948 by Ogier Ward, later from Bourque in 1954 and Watss in 1956 [16]. In this method, the prostatic capsule and bladder neck are open longitudinally. We have appreciated this and have adopted this method as a key and fundamental feature in our new operating technique.

Historically the first laparoscopic radical prostatectomy was performed and published by Schuessler et al. [2]. According to Delgado-Guerrero, 2016, the first case of laparoscopic simple prostatectomy, adenomectomy, was published by Dr. Mariano Mirandolino, who in 1999 performed the first adenomectomy of a 71-year-old man in Brazil through an extraperitoneal longitudinal incision of the prostate capsule [17]. Dr. Mariano Mirandolino is the pioneer of this operation. He published his 60 operated patients, but he did not describe the surgical technique in detail [24]. Autorino et al. published results from multicenter study and summarized that the laparoscopic simple prostatectomy was performed using different personal techniques developed based on the principles of transcapsular (Millin), transvesical (Freyer), or transvesicocapsular (Bourque) techniques, described for open simple prostatectomy. The

same author said that each investigator adopted specific operative strategies and technical moments to optimize this procedure [18]. We completely agree with this after our study of the literature on this topic. We find a lot of author's papers who present the simple prostatectomy on the principles of laparoscopy. They mainly describe the indications and results of the method without providing a detailed description of the surgical technique and the significance of each stage of it. We have not found another description of a laparoscopic method for simple prostatectomy that coincides with ours.

Obviously the laparoscopic simple prostatectomy is not difficult for an experienced laparoscopic urologist. More of cited authors mentioned their laparoscopic radical prostatectomy experience. From a review of literature, it can be seen that laparoscopic radical prostatectomy and laparoscopic simple prostatectomy began their development together [2, 3]. Probably due to standardized transurethral monopolar resection and classical open simple prostatectomy, laparoscopic simple prostatectomy develops more slowly. However, the lack of a consistent description of the details of the method does not allow it to be used for comparative training. The study of many different methods does not allow to create a true value and to standardize one of them. We classified the publications closest to our method according to the benchmarks of the operating technique, as it is shown in **Table 1**.

Therefore, we accept that operative methods published by other authors cannot serve for training. That is why we have decided to describe our new method in detail by comparing it to a similar one in prostate cancer, which is widely used, endoscopic extraperitoneal radical prostatectomy (EERPE) [8]. We have not found another description of a laparoscopic method for simple prostatectomy that coincides with ours. There is one method with abbreviation similar to ours but in fact is completely different [34]. So we did an innovative learning protocol. This protocol compares the EERPE surgical procedure to our adenomectomy surgical technique, EETAP. Moreover, training protocols for endoscopic extraperitoneal radical prostatectomy are found in the literature that can serve to build operator skills as a basis for our method [37–39]. According to the learning protocol of Stolzenburg JU, even residents without open surgery skills can perform EERPE after learning this protocol [40]. Thus, the operator's skills for one method can be applied to the other method, as shown in **Table 2**. Through it we believe that it is possible to introduce and standardize our method in practice.

The correlation ratio in **Table 2** between the two techniques shows that the skills for EREPE can be the basis for implementing EETAP. Moreover, this confirms our hypothesis for intraoperative conversion of adenomectomy into radical prostatectomy, if necessary. Mariano et al., 2006, reported a prostate biopsy in all 60 patients before being operated by laparoscopic simple prostatectomy [24]. Van Velthoven et al. [20], published in 11% of the operated patient's prostate cancer and three high-grade pin [26]. We have done prostate biopsy to four of our patients. Fortunately, we do not have a postoperative prostate cancer patient. None of the authors described behavior in patients with postoperative prostate cancer. Are they performing a second operation or applying another method? We assume that

our hypothesis for an intraoperative solution based on express histological examination in selected cases can solve this problem. The disadvantage of this hypothesis is the absence of a pathological preoperative stage, as is achieved in the puncture prostate biopsy. We also offer a second hypothesis for preoperative differential diagnosis of prostate cancer suspected patients by performing a noninvasive urine test SelectMDx [41, 42]. This test is popular as a liquid biopsy because of its high negative predictive value for aggressive prostate cancer with Gleason score of 7 to 10. The test is recommended of prostate cancer diagnosis in the European Urological Guidelines for 2018 [43]. We introduced this test in our daily practice since November 2017 [12]. The negative predictive value of the test is 98% for prostate cancer Gleason score 7, 99% for Gleason scores 8–10. Thus, this test can be the modern solution for preoperative diagnosis. Via SelectMDx test, patients who are candidates for BPH surgery can minimize incidental cancer to 8% or less and could replace the preoperative classical prostate biopsy. We cannot prove this hypothesis at this new indication due to lack of enough cases from our practice. However, this new hypothesis may be the basis for a prospective study to determine a new indication for this urine test. Patients receiving 5-alpha reductase inhibitors as well as those with a permanent urethral catheter are contraindicated or not be able to this method.

## 7. Conclusion

The operative treatment of urinary symptoms of benign enlarged prostate is performed with the main purpose of achieving satisfactory spontaneous urination for the patient. Our main motive is to find and describe a surgical method that protects the urethra from damage and brings to the patient the benefits of the open simple prostatectomy without its complications. Various surgical techniques for laparoscopic simple prostatectomy are found in the literature. Published cases are a bit about world practice. The world's largest urological recommendations do not define a proven method for laparoscopic simple prostatectomy. There is no detailed description of a method to be adopted and standardized. For the first time in the literature, a surgical method of endoscopic extraperitoneal transvesicocapsular adenomectomy of the prostate (EETAP) is discussed and published. This method may be performed by an operator with experience in endoscopic extraperitoneal radical prostatectomy according to our innovative learning protocol in this respect. In our opinion, this new method, its detailed description, its abbreviation, the innovative protocol for its application, and the new diagnostic hypotheses can serve as a basis for multicenter studies and conclusions for its standardization in the broad urological practice.

## Conflict of interest

The author declares no conflict of interest.

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Chapter 7

# Reduced Port Extraperitoneal Laparoscopic Radical Prostatectomy

Kazuhiro Araki and Yukio Naya

**Abstract**

Robot-assisted laparoscopic prostatectomy (RALP) is more popular than laparoscopic radical prostatectomy (LRP) in twenty-first century. However, RALP is still an expensive surgery. Open radical prostatectomy (ORP) was a gold standard and not an expensive surgery. However, ORP is not minimum invasive. LRP is relative expensive and minimum invasive. The problem of RALP or LRP is necessary to spread the wound for removing prostate and the pain of wound is often a problem. Using U-shaped incision at umbilicus, spreading the wound is not necessary to remove prostate. Single-port surgery is a challenging procedure for surgeons in spite of faster recovery and higher patient satisfaction than conventional laparoscopy. Adding one or two port, reduced port surgery is easier than single-port surgery. Reduced port LRP is an extension of conventional LRP. The procedure is as same as conventional LRP. Curved or flexible instruments are not always necessary in the reduced port LRP. Reduced port LRP has less pain and better cosmetics than conventional LRP because the prostate is removed from the umbilicus. It is not necessary to spread the wound for removing prostate.

**Keywords:** reduced port LRP, conventional LRP, umbilicus, EZ access

## 1. Introduction

Nowadays, robot-assisted laparoscopic prostatectomy (RALP) is more popular than laparoscopic prostatectomy (LRP). However, RALP is a most expensive surgery. The overall cost consequence of RALP was estimated at an additional €2459 (95% CI 1377–3540, p = 0.003) as compared with ORP and an additional €3860 (95% CI 559–7160, p = 0.031) as compared with LRP [1]. Rabenalt et al. reported single-port LRP in 2010 and Amin et al. and Cáceres

et al., reported in 2011 and 2012 [2–4]. Single-port surgery leaves little to no scarring and may reduce complications that commonly occur after traditional open and even traditional laparoscopic abdominal surgery. Patients are reporting less discomfort and faster recovery compared with those undergoing traditional laparoscopy. Tugcu et al. reported that single-port pyeloplasty can offer faster recovery and higher patient satisfaction than conventional laparoscopic pyeloplasty [5].

Ca'ceres et al. reported their 31 case of single-port LRP. In their results, mean operative time was 207 min and mean estimated blood loss was 258 ml. The average length of stay was 2.9 days and visual analog pain score (range: 0 [no pain] to 10) at day 2 was 1.2. Five focal positive margins (16.7%) were encountered. Major complications occurred in two patients (6.5%) (hypercapnia with respiratory acidosis and rectourethral fistula) and minor complications in four (12.9%) (atrial fibrillation, orchitis, transfusion, and vomiting). No case required additional analgesia. Thus, single-port LRP might be a safe procedure for skillful surgeon. However, for common surgeons, the single-port approach is more challenging than traditional laparoscopy because the surgeon has less freedom of movement with all instruments using the same entry point. Specially designed flexible instruments help to overcome that limitation. Sato et al. reported that 469 single-site surgeries were carried out between February 2009 and December 2012 at nine academic institutions in Japan. Radical prostatectomy was carried out in only six cases [6].

However, adding one or two port, reduced port surgery is easier than single-port surgery. Reduced port LRP is an extension of conventional LRP. The procedure is as same as conventional LRP. Recently, we perform several reduced port laparoscopic surgery, such as pyeloplasty, partial nephrectomy, excision of urachal remnant, and prostatectomy. We start reduced port LRP from April 2018. In this chapter, we introduce reduced port LRP. Reduced port LRP has less pain and better cosmetics than conventional LRP. It is not necessary to spread the wound for removing prostate.

## 2. Reduced port LRP

### 2.1. Indications

Radical prostatectomy (RP) is an appropriate therapy for any patients with clinically localized prostate cancer that can be completely excised surgically, who has a life expectancy of 10 years and more and has no serious conditions that would contraindicate an elective operation.

The indications for laparoscopic RP (LRP) are same as that of open radical prostatectomy.

Absolute contraindications to laparoscopic prostatectomy include the inability to undergo general anesthesia or uncorrectable bleeding diatheses.

Patients who had a history of inguinal mesh herniorrhaphy, or primary transurethral resection of prostate (TURP) 3–4 months before LRP, is not an indication of extraperitoneal LRP. Inguinal hernia repair with the incorporation of prosthetic mesh has been reported to create a dense, fibrotic reaction, complicating future pelvic procedures [7]. There have been several reports of surgeons encountering severe fibrosis and scarring during RRP in patients who have

undergone prior mesh hernia repairs, leading to early termination of the procedure [8–10]. Recent several studies have reported that transperitoneal LRP after prior laparoscopic inguinal herniorrhaphy is feasible and does not adversely affect operative and functional results [11–13]. In my experience, adhesions and distortion of normal anatomy is a serious problem of performed extraperitoneal prostatectomy. It is better to consider transperitoneal approach.

Capsular perforation during TURP and extravasation of the irrigation fluid might be periprostatic fibrosis. Fibrosis of the previously resected bladder neck may lead to worse healing at the anastomosis [14, 15]. Menard et al. compare the morbidity and functional results after laparoscopic radical prostatectomy with and without previous TURP [16]. They performed LRP at least 3 months after TURP. They concluded LRP after TURP can be performed without compromising the radical nature of cancer surgery. However, the procedure is associated with worse intraoperative and postoperative outcomes with respect to operative time, length of catheter stay, length of hospital stay, and surgical complication rate. Gellhaus et al. reported the results of RALP after HoLEP. According to their report, the posterior bladder neck and apical dissections were significantly more challenging in the setting of previous HoLEP [17].

### 2.2. Informed consent

As with open surgery, patients must be counseled on the risk of adjacent organ injury, such as ureter, rectum, bladder, and iliac vessels. Patients undergoing LRP must be aware of the potential for open conversion. The risk of general anesthesia should be presented to the patients.

### 2.3. Bowel preparation

Considering the risk of rectum injury, a preoperative bowel preparation may be used. The patient diet is limited to clear liquids only after 21'o clock the day before surgery. An enema administered the morning of surgery is recommended. A broad-spectrum antibiotic is administered intravenously 30 min before surgery.

### 2.4. Patient positioning

The patient is placed in a supine position in slightly Trendelenburg with arms tucked and padded at the sides. Open radical prostatectomy (ORP) was high risk of deep venous thrombosis (DVT). The risk of DVT in LRP is low. However, pelvic lymphadenectomy (PLND) is a risk of DVT in spite of laparoscopic surgery. Sequential compression stocking devices are placed on both legs and activated before surgery. To allow for the access to the rectum, patient's legs are spread apart.

### 2.5. Surgical technique

#### *2.5.1. Trocars insertion*

A right-handed surgeon stands on the left side of the patient. A U-shaped incision is placed on the lower edge of the umbilicus, the subcutaneous fat is divided by the muscle hook, and the rectus abdominal muscle is bluntly peeled off. It is easy to access the space between

urachal duct and posterior rectus sheath. Middle finger or index finger is inserted and bluntly peeled off to the arcuate line. A balloon dilator device (PDB balloon, A balloon dilator device (PDB balloon, Coviden Autosuture, Mansfield, MA) is inserted into the preperitoneal space and advanced down to the pubis along the midline. Approximately 500–900 ml of the air is inflated to develop the space of Retzius under direct vision of flexible 5 mm endoscope inserted through the balloon trocar. After removing the balloon trocar, special multi-lumen access device was put in the umbilical incision. Various different devices exist of single-port access, including the GelPort (Applied Medical, Rancho Santa, Margarita, CA), the TriPort (Advanced Surgical Concepts, Bray), and EZ access (Hakko Co. Ltd., Tokyo). Usually, we used EZ access oval type (Hakko Co. Ltd., Tokyo). The cost of EZ access is only $75.7. For example, the price of GelPort is $299.00. A 12 mm and a one 5 mm trocar are inserted into EZ access (to consider cost, reusable trocar is better). Start pneumoperitoneum at 10 mm Hg; 3 mm or 5 mm trocar is inserted into the left lower abdomen (right-handed surgeon) or the left lower abdomen (left-handed surgeon), and next 5 mm trocar is inserted into middle lower abdomen. If necessary, 3 mm or 5 mm port is inserted opposite side of lower abdomen (**Figures 1** and **2**).

*2.5.2. Development of Retzius cavity and endo-pelvic fascia incision*

The fat in front of prostate is removed from prostate. Anterior surface of prostate is revealed until the deepest of Retzius cavity. Endo-pelvic fascia is incised along both outsides of the prostate gland and the rectal pre-fat is exposed on the dorsal side (**Figure 3**). Preventing inguinal hernia, peritoneum is dissected from seminal duct and vessels.

*2.5.3. Dissecting of bladder neck and cutting*

The fat outside the bladder prostate boundary is removed as much as possible. The shape of bladder neck is revealed (**Figure 4**) and lateral part of the seminal vesicles is identified before

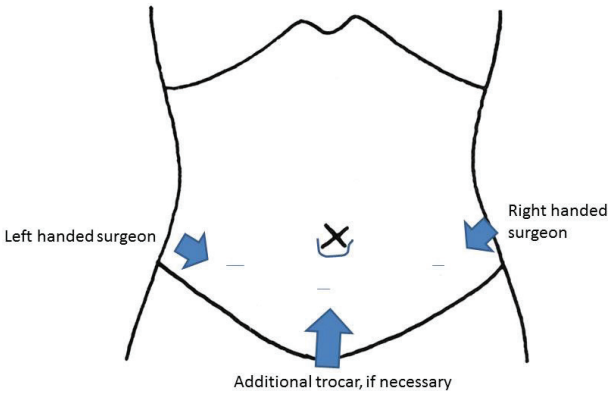


**Figure 1.** Schema of trocar placement.

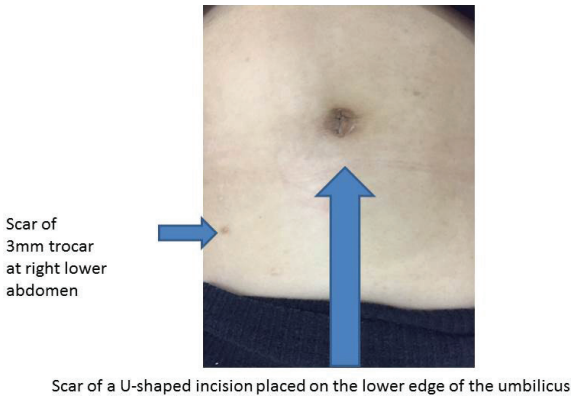


**Figure 2.** A picture of operative scars after surgery.

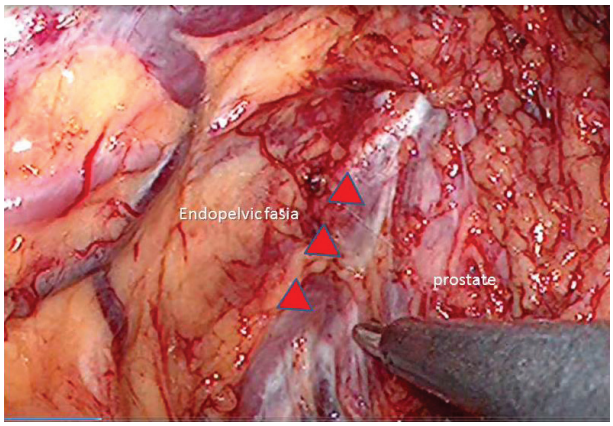


**Figure 3.** Cutting of endo-pelvic fascia.

bladder neck cutting. Cutting after the internal urethral meatus (**Figure 5**), the vas deferens is identified and cut (**Figure 6**).

*2.5.4. Denonvilliers' fascia incision and cutting the prostatic lateral ligament*

After dissection of the seminal vesicles from bladder, the seminal vesicles and the vas deferens are lifted up, the Denonvilliers' fascia was incised carefully. The space between the rectum and the prostate is dissected at the midline. The prostatic lateral ligament remaining on the prostate outer side is coagulated and cut (**Figure 7**). It is easy to use a sealing device to proceed without switching the device. To avoid rectal injury, it is important to take care of the line of cutting prostate lateral ligament.

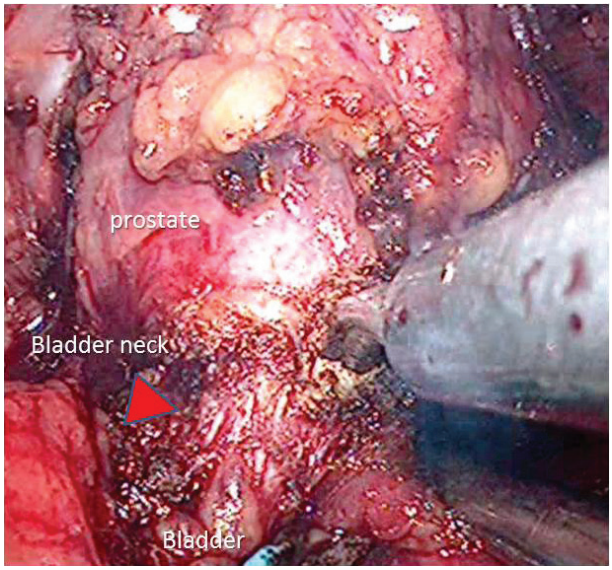


**Figure 4.** Incision of bladder neck.

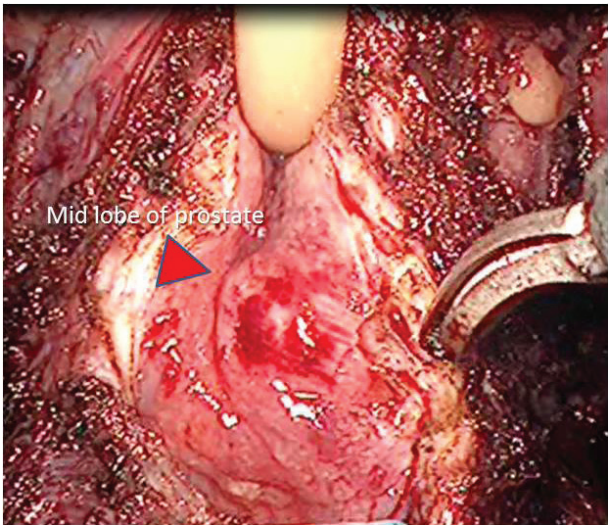


**Figure 5.** Cutting internal urethral meatus.

When preserving neurovascular bundle, to avoid heat damage, use 5 mm clip and cut with scissors. After cutting the lateral ligaments, the lateral side of urethra is identified.

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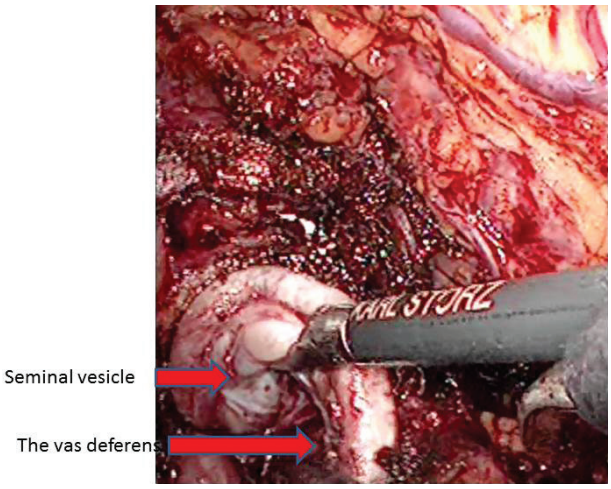


**Figure 6.** Identify of the vas deferens.

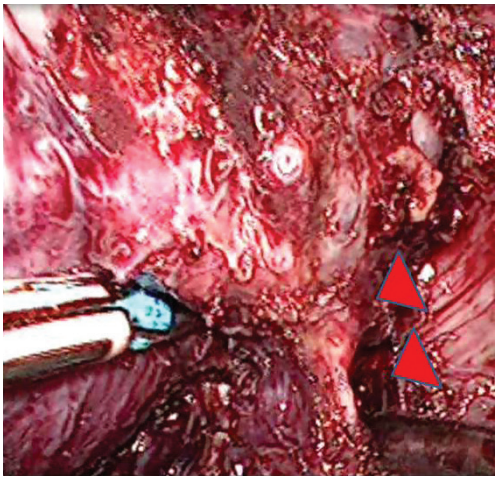

**Figure 7.** The prostatic lateral ligament.

### *2.5.5. Bunching and cutting of urethra*

Bunching of the DVC with Z suture was done (**Figure 8**). After cutting the DVC proximally, prostate is connecting to the pelvic floor only with the urethra (**Figure 9**). The urethra is cut as much as possible to preserve the urethra confirming the shape of the prostate. The bag is inserted from the umbilicus port, the prostate gland is stored in the bag, and prostate is removed from umbilicus port. If prostate is large, urachal duct is ligated and cut under umbilicus, it is easy to remove prostate. If lymphadenectomy is necessary, lymphadenectomy is done.

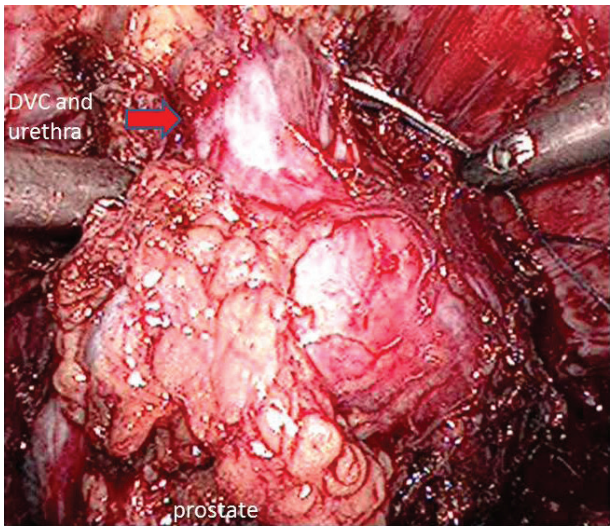


**Figure 8.** Bunching of DVC.

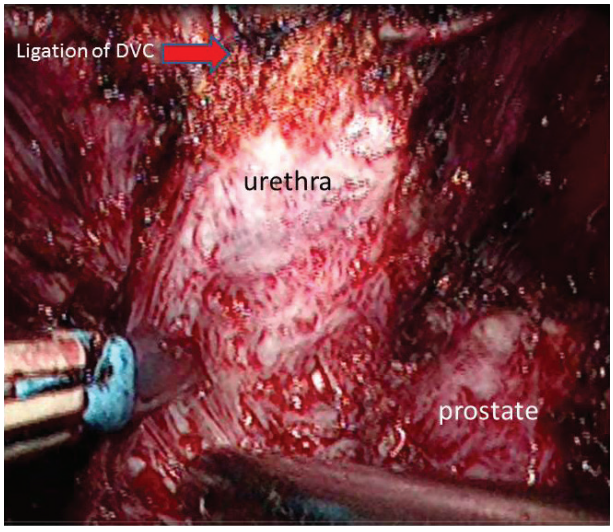


**Figure 9.** Revealed urethra.

*2.5.6. Pelvic lymphadenectomy*

Nowadays, lymphadenectomy for diagnosis is not necessary. For several patients with a significant risk for a nodal metastasis, PNLD may be useful for treatment.

Therefore, PLND is recommended in patients with intermediate or high risk.

To consider PLND, one more additional trocar is necessary, at middle lower abdomen. To retract the peritoneum, a 5-mm-sized retractor is inserted from the umbilicus port. Seminal duct and vessels are ligated and cut. Cooper's ligaments as a lower edge, adipose tissue is detached along external iliac vein and artery. The outside of LND is along the pelvic floor muscle. Obturator nerve and obturator artery and vein are exposed, and dissection is promoted to the inner iliac artery bifurcation. Next, carefully exfoliate the fat between the obturator vessels and the bladder. A thick lymph duct is treated with a sealing device or 5 mm clip.

*2.5.7. Anastomosis of bladder neck and urethral stump*

The bladder neck and urethral stump are anastomosed using 3-0 monofilament surgical suture at both ends. First, Rocco suturing is performed, after Rocco suturing (**Figure 10**), the rear wall is sutured with a horizontal mattress, and after closing it, the side walls are continuously sewn as they are. Approximately 10 needles are sewn. Place the urinary catheter in the bladder, inject saline, and check for leaks (**Figure 11**). Anterior bladder wall is fixed to pubic bone using 3-0 synthetic absorbable surgical suture.

*2.5.8. Drain insertion*

Incerting the forceps from the left trocar, the tip of the forceps is put the out side of umbilicus port. The end of drain is caught by the forceps and removed from the left trocar. The drain is placed. Usually, drain is removed 2 or 3 days after surgery.

Finally, the wound is closed with buried suture.

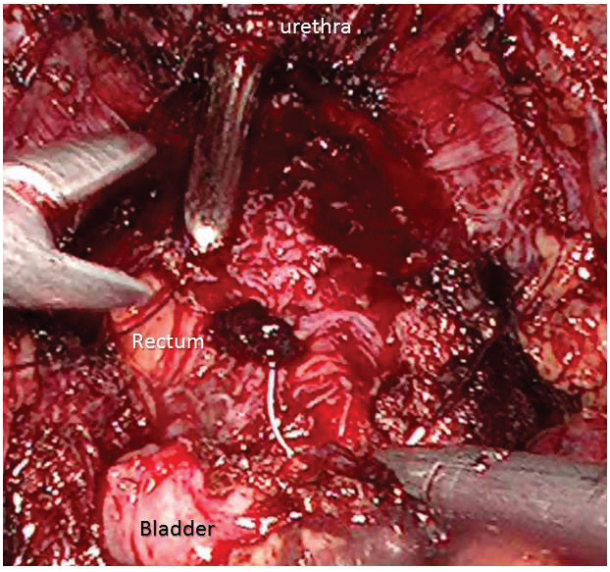


**Figure 10.** Rocco suturing.

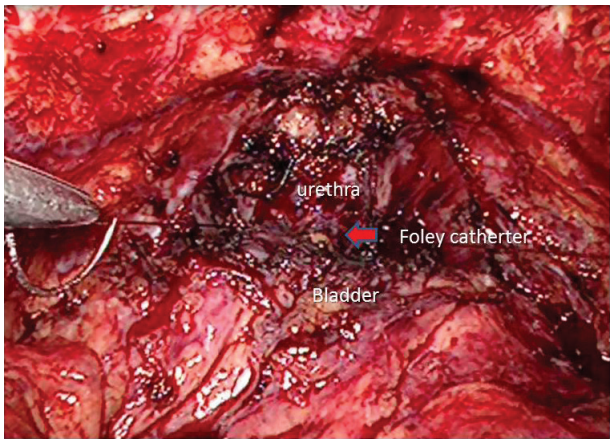


**Figure 11.** Anastomosis of urethra and bladder.

### 2.6. Complication

There is no prospective study to compare the efficacy and complication between LRP and reduced port LRP. We think that the quality of reduced port LRP is as same as conventional LRP, because surgical procedure is same. In our experience of LRP, rectal injury occurred in 1% of patients and allogeneic blood transfusion rate was 0% [17].

Rassweiler et al. compared early and late groups of LRP and an open radical prostatectomy group. Mean OR time was 218 min for late laparoscopic surgery and 196 min for open surgery. Transfusion rates were 9.6 and 55.7%, respectively. Complications included rectal injuries (1.4 vs. 1.8%), lymphoceles (0 vs. 6.9%), and anastomotic strictures (4.1 vs. 15.9%, respectively) [18]. Katz et al. reported the incidence of rectal injury is 2% during LRP [19]. Intraoperative recognition of rectal injury is important. When recognizing the rectal injury, multilayer primary closure should be performed before bladder and urethral anastomosis. Filling the water in front of rectum and injection of air into the rectum from anus to check the leaks. When fistula between vesicourethral anastomosis and the rectum, putting temporary artificial anus is necessary. After control of the infection, secondary reconstructive surgery using gracilis muscle flaps between rectum and vesicourethral anastomosis.

Injury of iliac vessels may be occurred during the lateral side trocar placement or along the path of instruments from the lateral side trocar.

The incidence of venous thromboembolism (VTE) of LRP and RALP is very low about 0.5%. However, PLND is the risk of VTE in spite of laparoscopic surgery. Tyritzis et al. reported that the risk of VTE in RALP is 7.52 times when LND is done [20]. The AUA guidelines and EAU guidelines do not recommend the use of prophylactic anticoagulants for LRP and RALP unless patients have known risk of VTE [21, 22]. The use of sequential compression stockings are recommended during the operative and postoperative period.

| | Reduced port LRP | ORP |
|---|---|---|
| No of patients | 2 | 2 |
| Age | 67.5 (63-72) | 72.5 (72-73) |
| PSA | 5.37 (4.73-6.00) | 4.88 (4.51-5.24) |
| GL score | 3+3 / 4+4 | 3+3 / 4+4 |
| Clinical T | T1c | T1c |
| Duration of surgery | 296 (275-317) | 249 (235-258) |
| Estimated blood loss | 225 ( 100-350) | 1602 (1562-1642) |
| No of using painkiller | 1 (0-2) | 5 (4-6) |
| Blood transfusion | None | None |
| Duration of hospital stay | 9 | 12 |
| Complication | None | None |

**Table 1.** Comparison between reduced port LRP and ORP.

Urinary stricture is rare. In our experience of LRP, the incidence urinary stricture is 2%. Continence rate of 6 months after surgery is 85.9% in our LRP series.

Complications related to patients positioning, such as pressure injury, are rare. To avoid pressure injury, careful padding of vulnerable body parts (the hips, the shoulders, the knees and the calves) is important.

Open conversion is rare, and it usually occurred during a surgeon's early experience with LRP.

From April 2018 to May 2018, four radical prostatectomies were performed. Two cases were reduced port LRP and others were ORP. Two cases done with ORP had a history of lower abdominal open surgery. The results of radical prostatectomy are shown in **Table 1**. The number of the use of painkillers was less in the patients with reduced port LRP than in those of ORP. Estimated blood loss was smaller in those of reduced port LRP than those of ORP. Hospital stay was shorter in reduced port LRP cases.

## 3. Discussion

The advantages of laparoscopic or robot-assisted radical prostatectomy were significantly decreased blood loss and decreased postoperative pain and shorter convalescence than that of open surgery in spite of similar oncological outcome. However, almost five incisions and one 4–5 cm incision are required. Each incision had a risk of pain, blood loss, internal organs injury, port hernia and infection. According to Chang et al., the number of using analgesic medicine is less in reduced port LRP group than conventional LRP group (3 vs. 19, respectively, $p = 0.0318$) [23]. In 2008, Kaouk et al. reported first laparoendoscopic single-site radical prostatectomy (LESS-RP), which was performed on four patients with low-risk prostate cancer [24]. All four cases were completed without conversion

to a standard laparoscopic approach, and the mean operative time for prostate excision and vesicourethral anastomosis was 3.25 and 1.1 h, respectively. One patient developed a rectourethral fistula that required surgical intervention. The authors concluded that LESS-RP is challenging but feasible. After their report, several studies had also proved its feasibility and safety [23, 25]. However, even with the use of laparoscopic curved or articulating instruments, significant "clashing" with both the camera and other instruments can increase operative times and require significant laparoscopic skills especially for intracorporeal suturing. To overcome the problems, we have focused on reduced port surgery. Akita et al. reported excellent results of 2-port RP comparing with conventional LRP [26]. However, the duration of surgery was longer in 2-port RP than conventional LRP (351.8 ± 72.4 min in 2-port RP and 286.5 ± 63.3 in LRP, P: $p = 0.0019$). Therefore, we performed three or four port RP using 3–5 mm trocar. The procedure is same as conventional LRP and clashing with both the camera and other instruments do not increase. To facilitate smooth instrument manipulation along with adequate visualization during laparoscopy, usually trocars are placed in triangular fashion. In our method, triangulation is kept during operation. We have used conventional straight laparoscopic instruments, such as dissectors, monopolar scissors and needle holders, Ligasure sealing device (Medtronic, Minneapolis, MN), WECK Hem-o-lok® ligation clip and applier (Teleflex Medical, NC), 5 mm flexible scope (Olympus, Tokyo). No other special instruments for LESS. The cost of reduced port LRP (single-port access, four trocars, sealing device) is as same as conventional LRP (five trocars, sealing device).

Hughes et al. reported RALP led to cost savings in the postoperative phase after surgery in a hospital when the cost of the index surgery was excluded. However, Hyldgard et al. reported the use of RALP generates a factor 1.3 additional cost when compared with OP and a factor 1.6 additional cost when compared with LP, on average, based on 12 months follow-up [1]. The median direct cost of RALP is $6752 and that of LRP is $5687. The main difference was in surgical supply costs for each procedure ($2015 for RALP, $725 for LRP) and operation room costs ($2798 for RALP, $2453 for LRP, $1611) [27]. Thus RALP is expensive.

Several authors reported Robot LESS [28–31]. However, it is necessary to buy new da Vinci surgical system for single-port surgery only. It is impossible now because Robot LESS is too expensive surgery however, in the future, Robot LESS become new standard single-port laparoscopic surgery.

## 4. Conclusion

The procedure of reduced port LRP is the same as conventional LRP. Blood loss is minimal due to tamponade effect of the pneumoperitoneum. The cost of reduced port LRP is cheaper than that of RALP. VTE, rectal injury, and transfusion are rare events. There is no prospective study to compare conventional LRP or RALP with reduced port LRP. Furthermore study is necessary.

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## Conflict of interest

We have no conflict of interest.

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Chapter 8

# Preventing Erectile Dysfunction after Radical Prostatectomy: Nerve-Sparing Techniques, Penile Rehabilitation, and Novel Regenerative Therapies

Michael Whalen

**Abstract**

Erectile dysfunction is a known and much-dreaded functional consequence of radical prostatectomy. Dr. Patrick Walsh pioneered the nerve-sparing radical retropubic prostatectomy in the early 1980s, which has mitigated the morbidity of this surgery. Post-operative potency rates range widely from 20 to 80%, however, and depend on myriad factors including age, preoperative potency, and degree of nerve-sparing during surgery. Over the past four decades several developments have continued to offer hope to patients and clinicians alike, including refined understanding of cavernosal nerve neuroanatomy, beneficial modifications in surgical technique, as well as the advent of robotic surgery. Furthermore, multiple pre- and post-operative penile rehabilitation techniques using mechanotherapy and pharmaceuticals have also improved functional recovery. This paper examines erectile dysfunction as a consequence of radical prostatectomy, including the physiology of erections, the pathophysiology of post-operative erectile dysfunction, novel surgical techniques to enhance neurovascular bundle preservation, and penile rehabilitation strategies involving hyperbaric oxygen, neuroprotective pharmaceuticals, dehydrated human amnion-chorion membrane allografts, and mesenchymal stem cell therapy.

**Keywords:** erectile dysfunction, nerve-traction injury, nerve-sparing radical prostatectomy, penile rehabilitation, amnion-chorion membrane therapy, stem cell therapy

## 1. Introduction

Erectile dysfunction is a known and much-dreaded functional consequence of surgery for prostate cancer. Although surgeons may cite oncologic control as the paramount component of the

"Trifecta" (i.e. cancer cure, continence, and potency), many patients cite recovery of erectile function as the true measure of treatment success. In the early days of radical prostatectomy, post-operative potency rates were poor, and in fact largely non-existent. With the advent of nerve-sparing anatomic radical retropubic prostatectomy, a surgical approach pioneered by Dr. Patrick Walsh, the prospect of post-operative recovery of potency became not only a possibility but a reality for many men. The myriad factors that influence a patient's likelihood of sexual function recovery after both open and robotic radical prostatectomy have been examined and published in the literature. Also, there has been much investigation into the pathophysiology of iatrogenic erectile dysfunction (i.e. neurapraxia and nerve-traction injury) in the form of in vitro, pre-clinical animal studies and even translational studies with randomized human subjects. Given the pivotal importance of erectile function in a patient's perceived post-operative quality of life, there is much interest in the optimization of perioperative techniques to spare the integrity of the cavernous nerves and to develop efficacious mechanical and pharmacologic penile rehabilitation programs. Such programs employ an increasingly sophisticated arsenal of medical technologies such as pluripotent stem cell therapy, cytokine-rich human amnion-chorion membrane allograft, and even reappropriation of pharmacotherapies traditionally used for other disease states that have been found to have neuroprotective properties. This chapter will examine the evolution in the understanding of erectile dysfunction as a consequence of radical prostatectomy and examine novel strategies for prevention and amelioration of this condition.

## 2. Physiology of erections

### 2.1. Anatomy

The central role of smooth muscle dynamics in the corpora cavernosa in the development of erections was first elucidated in the 1980s [1]. Identification of nitric oxide (NO) as the principle neurotransmitter for tumescence and phosphodiesterases for detumescence were also major milestones with well-known pharmacologic ramifications. Anatomically, beneath the Buck's fascia, the corpora cavernosa are surrounded by the two-layered tunica albuginea, a reticulated network of collagen and elastin fibers that provides structural support during tumescence. The outer layer serves to compress the obliquely oriented emissary veins during tumescence that results in the "bottle-neck" effect of slower outflow than inflow that is essential for maintenance of an erection (**Figure 1**) [2]. The penile arterial supply arises from internal pudendal artery, which then gives rise to the common penile artery that branches into the dorsal, cavernous, and bulbourethral arteries. The cavernous arteries are responsible for the engorgement of the corpora cavernosa during tumescence. Accessory pudendal arteries may also be present in up to 4–25% of patients and these arise from the external iliac, obturator, vesical, and femoral arteries. Their preservation has been shown to be important for recovery of erectile function after radical prostatectomy [3, 4].

### 2.2. Neuroanatomy

The vasomotor tone of the cavernous arteries is regulated by the autonomic cavernous nerves. They are the nerves that are being described during "nerve-sparing" techniques during radical

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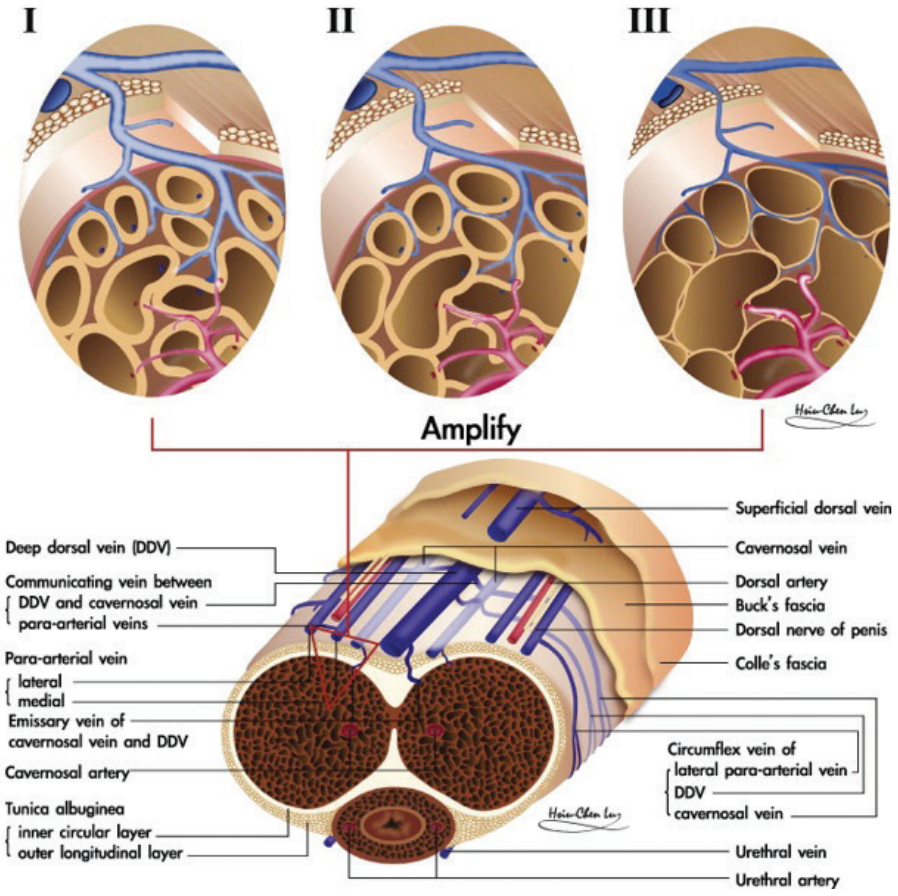


**Figure 1.** Anatomy of subtunical emissary veins as the basis for tumescence. Reprinted without changes from Molodysky et al. [2] https://creativecommons.org/licenses/by-nc-nd/3.0/.

prostatectomy. These nerves arise as an extension from the parasympathetic pelvic splanchnic nerves that originate from the pelvic plexus (S2–S4) located on either side of the rectum (**Figure 2**). These nerves innervate the endothelium of the cavernous sinuses and release acetylcholine which inhibits adrenergic neurons and stimulates NO release from endothelial cells [5]. NO increases intracellular production of cGMP with resultant decline in intracellular calcium and relaxation of the cavernous smooth muscle. Phosphodiesterase 5 is responsible for the degradation of cGMP and is the target of the well-known medications for erectile dysfunction.

Since Walsh and Donker pioneered the nerve-sparing radical prostatectomy in 1982, there has been much debate about the nature and trajectory of these nerves [6, 7]. These nerves have been found to travel as a latticework of delicate fibers principally along the posterolateral and lateral aspects of the prostate, but with some fibers coursing ventrally as well. Invaluable work in human cadavers by several investigators has elucidated precise position and orientation of these nerves to optimize their preservation during radical prostatectomy.

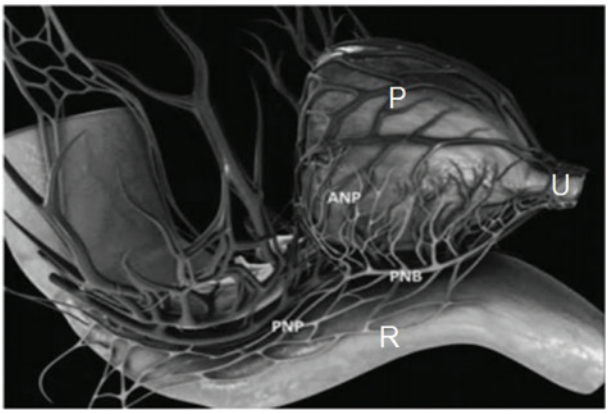


**Figure 2.** Pelvic plexus and cavernous nerve anatomy. P = prostate; U = urethra; R = rectum; PNP = proximal neurovascular plate; ANP = accessory neurovascular plate; PNB = predominant neurovascular bundle. Reprinted from Tewari et al. [12].

Costello et al. used cadaver models to identify three functional domains of the neurovascular bundle (NVB): the posterior and posterolateral component runs within the Denonvilliers' fascia and the pararectal fascia and innervates the rectum; the lateral component supplies the levator ani, and the cavernosal nerves lie along the posterolateral surface [8, 9]. Furthermore, Lunacek et al. showed that the cavernous nerves are displaced more anteriorly and splay along the lateral aspect of the prostate like a curtain [10]. These findings inspired the "curtain dissection" technique of high anterior release as well as the technique of preserving the lateral prostatic fascia within which the neurovascular bundle travels known as the "Veil of Aphrodite" technique to maximize the number of nerve fibers preserved [10, 11]. Dr. Ashutosh Tewari has conceptualized the neuroanatomy as consisting of a tri-zonal neural architecture, comprised of the proximal neurovascular plate (PNP), predominant neurovascular bundle (PNB), and accessory neural pathways (ANP) [12]. The PNP is synonymous with the pelvic plexus and the PNB is the traditionally described NVB, which is enclosed within the layers of levator fascia and/or lateral pelvic fascia. The nerves are situated in a "hammock-like" distribution rather than a distinct, isolated structure (**Figure 2**).

Further anatomical studies have demonstrated that a significant proportion of the nerves are situated on the anterior surface of the prostate, 21.5–28.5% [13] and 19.9–22.8% (**Figure 3**) [14]. Structural configurations range from round and bundle-like to more widely distributed splay-like [15]. Ganzer et al. employed computerized planimetry software to analyze the topography of the nerves on whole-mount pathologic sections obtained during non-nerve-sparing radical prostatectomy [16]. Total nerve surface area was most concentrated dorsolaterally (74.5–84.1%), but up to 39.9% of nerve surface area was found ventrolaterally. These correspond to the ANPs described by Dr. Tewari's group, who found them in 41% of the cadavers [12]. It is possible that all of these nerves are not responsible for erections. Subsequent studies in electrophysiologic stimulation have shown cavernosal pressure responses with stimulation at all positions of the midprostate between the 1:00 and 5:00 positions for all patients, suggesting their role in potency [17]. The precision vs. degree of electrical spread of such electrical stimulation may represent a limitation of this testing. Conversely, Costello et al. reported that

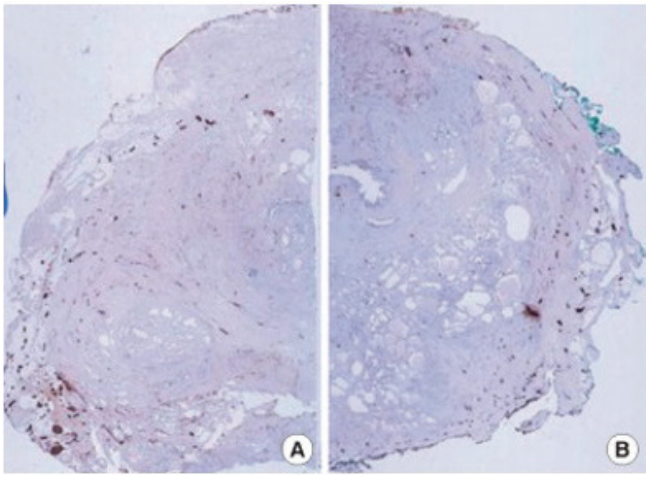


**Figure 3.** Whole-mount anatomy of neurovascular bundle (NVB) topography on the prostate. A. NVB concentrated at posterolateral aspect of prostate (S-100 stain) B. NVB are more widely distributed to ventral aspect of prostate (S-100 stain). Reprinted from Lee et al. [14].

significantly parasympathetic nerve fibers only account for 4–6.8% of nerves on the anterolateral aspect of the prostate [18]. These findings were corroborated by Ganzer et al., who used immunohistochemistry to distinguish between parasympathetic and sympathetic nerves. They reported that only 14.6% of the parasympathetic nerves resided above a horizontal line drawn at the prostate base and only 1.5% above a horizontal line at the apex [19].

How these anatomical findings impact the functional outcomes of the various nerve-sparing approaches described below, some of which advocate for high anterior release of the prostatic fascia, is interesting to consider (see Section 5.2).

## 3. Pathophysiology of post-prostatectomy erectile dysfunction

There are several acute and chronic factors that contribute to decline in erectile function after surgery for prostate cancer. These factors may be classified as vasculogenic, neurogenic, and even psychological. The burden of cancer diagnosis, treatment, and need for long-term PSA monitoring, along with recovery from surgery, implications on self-image, awareness of mortality, and perceived or actual reduction in penile length represent a constellation of psychosocial factors that may contribute to ED.

The role of accessory pudendal arteries in vasculogenic erectile function has been described above. Chen et al. has also implicated the veins that travel longitudinally within the layers of the tunica albuginea. His group have reported that ligation of the DVC during prostatectomy results in dilatation of these veins which results in veno-occlusive dysfunction [20].

The vascular sequelae of radical prostatectomy were investigated by Mulhall et al., who reported cavernosometry and/or penile duplex ultrasonography [21]. They found arterial

insufficiency in 59% and venous leakage in 26% of men after bilateral nerve-sparing RRP who had excellent pre-operative erectile function. Normal vascular status was found in 35% of men. Return to penetrative function was correlated with the vascular status, with 47% return if normal status, 31% in arteriogenic insufficiency, and only 9% with veno-occlusive dysfunction at 12 months. They also reported that the longer the duration of erectile dysfunction, the higher the risk of venous leakage. Zelefsky et al. reported venous leakage in 52%, arterial insufficiency in 32%, and neurogenic dysfunction in 12% [22]. Montorsi et al. found a higher proportion of patients with veno-occlusive disease in their randomized study of intracavernous alprostadil after open RP: 67% veno-occlusive dysfunction, 17% arterial insufficiency, 17% normal vascular dynamics [23].

### 3.1. Neurapraxia

The neurogenic basis for erectile dysfunction implicates the cavernous nerve architecture. Preservation of these architectural substrates may not be sufficient alone to engender recovery of post-operative function, as suggested by the well-documented latency period between surgery and functional recovery. This latency ranges from 6–24 months and has been suggested to be the result of nerve-traction injury from the physical manipulation/handling during surgery and resultant neurapraxia and axonotmesis [1, 24, 25].

Intraoperative manipulation and injury to the cavernosal nerves results in hemodynamic and histologic changes within the penis, which manifest clinically as erectile dysfunction. This injury may result from mechanical or thermal sources. Iatrogenic traction on the delicate neurovascular tissue can cause-stretch induced nerve injury and resulting dysfunction. Neuropathies may be classified into three histologic groups: neurapraxia, axonotmesis, and neurotmesis. Neurapraxia is the least severe and is characterized intact neural structural elements, but there may be ischemia and/or demyelination which leads to signal conduction block. Functional deficits in peripheral nerves manifest as motor, proprioceptive, and soft touch deficiencies, but these usually resolve in a few weeks (up to 12 weeks) [26]. The next level of injury is axonotmesis in which axons and their myelin sheaths over long segments of nerve are disrupted, while supporting structures such as the endoneurium are left intact [27]. There is consequent Wallerian degeneration distal to the level of injury and proximal axonal degeneration to the next node of Ranvier. Since the endoneurial tubes remain intact, recovery should be complete after a matter of several months but may not be complete. Frank transection of the nerve is termed neurotmesis, in which the endoneurial tubes and connective tissue components are disrupted. Intraneural fibrosis develops and impairs axonal regeneration and thus inhibits nerve functional recovery. Peripheral nerve regeneration is mediated by multiple factors including neurotrophic factors, extracellular matrix, and intact cellular components of the nervous system (i.e. endoneurium) [28]. Tissue trauma from surgery also generates an inflammatory response and oxidative stress around the degenerating axons with results in chromatolysis (degradation of the protein synthesizing infrastructure of the neuronal cell body) [29].

Nerve injury may have a vasculogenic etiology as well. Nerve ischemia may be a result of direct compression injury or stretch (“traction”) injury, which produces a reduction in cross-sectional

area and resultant compression of the vasculature [27]. Traction disrupts and occludes small-sized arteries traveling with the nerves (vasa nervorum) which supply pelvic tissues as well as the nerves themselves. Biochemically within the cavernosal smooth muscle cells, hypoxia induces production of superoxide which initiates oxidative reactions and attacks surrounding molecules to produce more free radicals. Oxygen free radicals in the setting of a nitric-oxide containing environment tends to combine to form peroxynitrite (O═NOO-) which is highly neurotoxic. Exposure of nerves to this compound leads to rapid excitation, excitotoxicity, and degeneration in the acute setting. Nitric oxide bioavailability is thereby reduced in this setting, which further impacts penile smooth muscle relaxation and exacerbates the hypoxic conditions.

### 3.2. Thermal injury

The importance of athermal dissection has been reinforced as classic teaching during nerve-sparing radical prostatectomy. The precise functional deficits induced by monopolar or bipolar cautery has been investigated in a canine model [30]. A total of 12 dogs were divided into four groups of neurovascular bundle dissection: Group 1, suture ligatures; Group 2, monopolar electrocautery; Group 3, bipolar electrocautery; Group 4, ultrasonic shears. Peak intracavernous pressures in response to distal cavernous nerve stimulation immediately post-op and at 2 weeks showed an attenuated response compared to controls (74–91% decrease and 93–96% decrease, respectively). In the dogs where electrocautery was employed, there was in fact almost no rise in the intracavernous pressure in response to stimulation. The findings in this study were presented in the context of having spared the contralateral neurovascular bundle from any dissection. Their results may have been even more dramatic if thermal energy had been used bilaterally. The follow-up was also admittedly short in this series at 2 weeks post-op only. Much longer durations at 6-, 12-, and even 24 months would be helpful to determine the long-term impact of thermal energy on recovery of potency (see Section 5.6).

This very objective was explored in humans after robotic prostatectomy, demonstrating delayed recovery after 12–18 months, but with 68% of bilateral nerve-sparing patient ultimately recovering function at 24 months [31] (see Section 5.3).

### 3.3. Chronic cavernosal tissue changes

In the chronic phase of injury, the persistent loss of nerve signal conduction results in loss of spontaneous nocturnal erections and relative cavernosal ischemia. The pathophysiologic consequence is cavernosal smooth muscle apoptosis, upregulation of TGF-beta and collagen deposition within the corpora [32–35]. Cavernous neurotomy studies in rats have demonstrated that corporal smooth muscle apoptosis begins 1 day after injury and peaks within the first week [34]. This fibrotic reaction impairs full expansion of the venous sinuses within the tunica and failure to adequately compress the emissary veins against the tunica. The result is “veno-occlusive dysfunction” in which the venous outflow occurs with the same velocity as arterial inflow. In this setting, tumescence is unable to be achieved or maintained. Furthermore, there is anatomical loss of penile length and girth as a result of the cavernosal smooth muscle fibrosis.

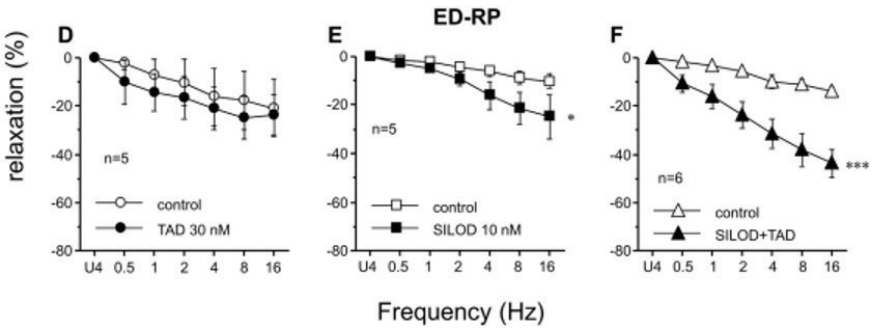


**Figure 4.** Effects of tadalafil, silodosin, or their combination on neurogenic relaxations induced by electrical field stimulation in human corpus cavernosum strips obtained from patients with erectile dysfunction after RP (ED-RP). *P < 0.05, *** P < 0.001. Reprinted from Martinez-Salamanca et al. [41].

### 3.4. Sympathetic disinhibition

Erectile function is not only the result of parasympathetic input, but a dynamic interplay between enhanced parasympathetic and inhibited sympathetic function. The role of adrenergic, sympathetic signals in ejaculation and detumescence have been well-established [36]. The adrenergic system essentially inhibits tumescence via the release of presynaptic norepinephrine (NE) that binds to postsynaptic $\alpha$1- and $\alpha$2-adrenergic receptors that induce penile arterial and cavernosal smooth muscle contraction. Also, the activation of presynaptic adrenergic receptors on the parasympathetic nerves inhibits release of NO [37]. The $\alpha$1 receptor subtype is predominant in human erectile tissue, and furthermore $\alpha$1A and $\alpha$1D are more common than $\alpha$1B in humans [38, 39]. Neurogenic contractile responses have been shown to be increased in the corpus cavernosum from rats after cavernous nerve injury and in cavernosal tissues from men with post-prostatectomy ED [40].

Recent animal studies have elucidated the role of adrenergic function on the contractile dynamics of cavernosal smooth muscle [41]. After bilateral crush injury to the cavernosal nerves rats were administered phentolamine (non-selective alpha-blocker), silodosin ($\alpha$1A-selective alpha-blocker), or tap water only for 4 weeks and intracavernosal pressure (ICP) was monitored after (1) electrical stimulation of the cavernosal nerve proximal to the region of injury and (2) IV administration of tadalafil (phosphodiesterase 5 inhibitor). A significantly greater increase in ICP was observed for the silodosin group compared to the phentolamine or tap water groups after both electrical stimulation alone and co-administration with IV tadalafil. These findings suggest therapeutic benefit to alpha blockade for recovery of erectile function after RP. The authors translated their experiments to humans by obtaining strips of cavernosal smooth muscle at the time of inflatable penile prosthesis insertion. The response to electrical stimulation ex-vivo was enhanced by pretreatment of the muscle strips with both silodosin and tadalafil compared to tadalafil alone (**Figure 4**) [41].

## 4. Epidemiology of erectile dysfunction

The prevalence of erectile dysfunction in the general population has been reported by two large surveys: the Massachusetts Male Aging Study (MMAS) and the National Health and

Social Life Survey (NHSLS). According to the MMAS the rate of complete, moderate, and mild ED for the study of n = 1709 community-dwelling men in their 40–70 seconds was 5.1–15, 17–34, and 17%, respectively [42]. The NHSLS examined n = 1410 community-dwelling men and women in 1992 and reported rates of ED by age: 7%, 18–29 years; 9% 30–39 years; 11% 40–49 years; 18%, 50–59 years [43]. The definition of ED in this study was not quantified with validated questionnaires. International studies have reported rates of 20–40% for men 60–69 years [44]. ED is therefore an age-dependent disease. Other established risk factors include diabetes mellitus, hypertension, hyperlipidemia, psychiatric/psychologic disorders, history of pelvic trauma, chronic disease states (i.e. hypogonadism, thyroid disease, chronic kidney disease), and socio-demographic status.

There are multiple validated questionnaires to accurately assess various aspects of a patient's baseline sexual function. These questionnaires are integral in the patient workup as both a quantifiable measure of their function and a method of realistic prognostication of their likelihood of meaningful recovery. These elements comprise an important aspect of patient preoperative counseling and informed consent. The International Index of Erectile Function (IIEF) consists of 15 items and five domains and was developed by an international panel of experts for uses in determining treatment efficacy in clinical trials [45, 46]. Given its high sensitivity for detecting clinically significant treatment effects, it is regarded as the gold standard treatment outcome measure. Administration of this long questionnaire is somewhat cumbersome in a routine clinic setting, however. The National Institutes of Health's Consensus Panel on ED lead the development of an abridged five-item version of the IIEF, called the IIEF-5 or the Sexual Health Inventory for Men (SHIM). The SHIM is a powerful grading system and easily-administered patient reported tool [47]. It has high sensitivity and specificity and has been shown to be more reliable than a single item self-assessment of severity of ED [48]. Each question is rated on a Likert scale from 1 to 5, and consists of: "Over the past 6 months":

1. How do you rate your confidence that you could get and keep an erection?
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
5. When you attempted sexual intercourse, how often was it satisfactory for you?

Based on response to the questions, men may be categorized into one of five grades of ED severity: no ED (SHIM 22–25), mild (17–21), mild to moderate (12–16), moderate (8–11), severe (1–7). Although there have been multiple other questionnaires published—the Quality of Erection Questionnaire, the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS), the Self-Esteem and Relationship questionnaire (SEAR); the Erection Hardness Score (EHS), the Sexual Experience Questionnaire—the IIEF and SHIM are the most widely employed, and have indeed been translated into over 30 languages [49, 50]. Another popular health-related quality of life (HRQoL) questionnaire specific to prostatectomy patients is the

Expanded Prostate Cancer Index Composite (EPIC), which examines urinary, bowel, sexual, and hormonal domains [51]. Some of these validated instruments have been used to measure outcomes in the randomized penile rehabilitation studies (see below).

Studies of ED prevalence among men prior to undergoing radical prostatectomy report potency rates ranging from 43 to 84%; the 43% value was obtained through interrogation with the IIEF [52–54]. The landmark prospective Prostate Cancer Outcomes Study (PCOS) included n = 3533 men from the Surveillance, Epidemiology and End Results (SEER) cancer registries diagnosed with prostate cancer in 1994–1995. A total of n = 1288 men who underwent radical prostatectomy had completed a baseline questionnaire were included. Baseline erections firm enough for intercourse was 81%, with 49% reporting a least "little/some" difficulty in maintaining erections [52, 53]. A limitation of these figures, however, is the fact the FDA approval of sildenafil only occurred in 1998 and "baseline" function was assessed through post-hoc recall within 6 months after treatment in 90% of patients, thereby introducing recall bias.

### 4.1. Incidence of erectile dysfunction after radical prostatectomy

Recovery rates after bilateral nerve-sparing open RRP ranges from 31 to 86% of sexually active men with organ-confined disease [55]. The recovery rates for unilateral nerve-sparing range from 13 to 56%, and for non-nerve sparing 0–17% [56–60]. The CaPSURE database of community-based Urology practices has reported that only 20% of men return to preoperative baseline potency at 12 months after RP [61]. The metric for assessment has an impact on the incidence of ED, and the use of validated questionnaires such as the IIEF tends to expose higher incidence of ED [55]. The long-term outcomes of the PCOS study demonstrated [53] worse erectile function in men after RP compared to radiation therapy at the 2- and 5-year evaluation time points, odds ratio 3.46 and 1.96, respectively. There was no significant difference at the 15-year follow-up time point, however. Defining sexual function as "erections in sufficient for intercourse" produced absolute rates of ED at 2, 5, and 15 years of 78.8, 75.7, and 87%, respectively (**Figure 5**). Of note, only 14.5% of men underwent bilateral nerve-sparing surgery in this series.. Among men who had bilateral nerve-sparing, 5-year erectile function firm enough for intercourse was reported in 40% of men vs. 23% and 23% for unilateral nerve-sparing and no nerve-sparing, respectively. Age was a significant predictor on multivariable analysis. Some limitations were the late approval of sildenafil in 1998 and the fact that RP was performed in an open manner, which limits applications to modern series. During the 3 years prior to the 5 year evaluation, only 43% of men had tried sildenafil.

Contemporary robotic prostatectomy series demonstrate 12 month potency rates ranging from 70 to 80% [62]. A systematic review and meta-analysis of 15 case series totaling n = 3491 patients reported 12- and 24-month potency rates ranging from 54–90% to 63–94%, respectively [63]. Among patients who had bilateral nerve-sparing, 12- and 24-month potency rates were 74 and 82% respectively. There may be a learning-curve effect with the robotic prostatectomy outcomes as well. The impact of surgeon experience/learning has been reported, but did not demonstrate statistical significance for potency rates between cases 1–300, 301–500, and 501–700 (61, 63, 65%, respectively) [64].

Outcomes stratified by specific nerve-sparing approach are presented below (see Section 5.3 below).

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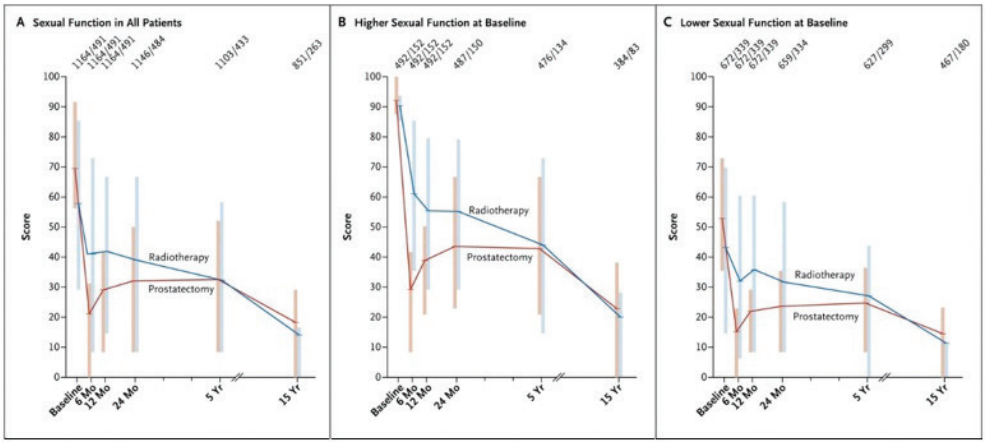


**Figure 5.** Sexual function over 15 years after treatment for prostate cancer. A. In all patients. B. Higher sexual function with International Index of Erectile Function (IIEF) score > or = 80; C. Lower sexual function, IIEF < 80. Numbers represent total of patients in radical prostatectomy (RP) group/radiation group. Reprinted from Resnick et al. [53].

### 4.2. Prognostic factors for recovery of erectile function post-prostatectomy

Factors for successful recovery of erectile function have been examined for patients after both open radical retropubic prostatectomy (RRP) and robotic prostatectomy in the modern era. A systematic review post-RRP identified age <60 years, completeness of nerve-sparing, and pre-operative sexual function [55]. Indeed, in the PCOS study a significantly higher proportion of men <60 years reported satisfactory response to sildenafil compared to older men ($p = 0.01$) [52]. The systematic review of robotic prostatectomy by Ficarra et al. cited age, baseline potency status, comorbidities index, and extent of nerve-sparing as predictors of postoperative recovery of potency [63]. There may be a learning-curve effect with the robotic prostatectomy outcomes as well. As discussed below, since nerve-sparing may be performed in an incremental manner rather than an "all-or-none" phenomenon, grade of nerve sparing has shown an influence on recovery [12, 65, 66] (see **Techniques of Nerve Sparing** below).

The impact of surgeon experience/learning has been reported [67], but did not demonstrate statistical significance for potency rates between cases 1–300, 301–500, and 501–700 (61, 63, 65%, respectively) [64]. As mentioned previously, lack of electrocautery during neurovascular bundle dissection portends earlier recovery of erectile function [31]. While other factors have been cited, the previous predictors are the most consistent throughout the medical literature.

Post-operative potency rates may be influenced by the time point of assessment. Studies typically report 12 and 24 month outcomes as the longest follow-up. Although recovery typically occurs within the first 2 years after surgery, delayed recovery is also possible. A series of n = 1003 men who underwent either open or robotic RP between 2007 and 2013 reported on the achievement of "good erectile function" as defined by IIEF-6 score ≥ 22 [68]. Among men with poor function at 12 months, the probability of recovering erectile function at 24, 36, and 48 months was 22, 32, and 40% on Kaplan–Meier analysis. The 12-month functional score and patient age were the only significant predictors of delayed recovery on multivariable analysis.

Also, very interestingly, the degree of nerve-sparing was not a predictor of delayed recovery; perhaps nerve-sparing only impacts early recovery at the 12-month time point. Surgical modality (open vs. robotic) was not explored. Similar findings of delayed recovery have been published in other reports [69, 70]. Such findings may be tempered by the gradual decline in erectile function after year 5 observed in the Prostate Cancer Outcomes Study [52].

## 5. Methods to improve nerve-sparing

### 5.1. Preoperative planning with multi-parametric MRI

Multiparametric magnetic resonance imaging (mpMRI) has gained widespread use in the workup of elevated PSA and diagnosis of prostate cancer via MRI-transrectal ultrasound (TRUS) targeted fusion biopsy. This technique has been shown to increase the detection rate of high-grade (i.e. Gleason 4 + 3 = 7) prostate cancer by 30% and result in lower detection of low grade prostate cancers by 17% [71]. The recently published PROMIS trial evaluated the performance of mpMRI to the reference standard template prostate mapping (TPM) biopsy and reported superior sensitivity for mpMRI compared to TRUS biopsy (93% vs. 48%, $p < 0.001$) and negative predictive value (89% vs. 74%, $p < 0.001$), allowing 24% with negative MRI to safely avoid having to undergo biopsy [72].

The utility of MRI may be applied to the domain of pre-surgical planning as well. The aggressiveness of nerve-sparing is not solely based on surgeon experience, but also on the anatomical location of the tumor and the presence of locally advanced (i.e. pT3a-b) disease that may be invading the neurovascular bundle. In the setting of pT3 disease (i.e. extraprostatic extension (EPE) and seminal vesicle invasion (SVI)), aggressive nerve sparing may result in a positive surgical margin (PSM), which has been associated with increased rates of biochemical recurrence, systemic metastasis, and prostate cancer-specific mortality post-prostatectomy, especially for high grade disease (i.e. Gleason Score 8–10) [73]. Even with careful adherence to surgical technique and the use of intraoperative frozen section analysis, microscopic positive margins may be imperceptible during surgery. A meta-analysis of 75 studies comprising 9796 patients who underwent mpMRI between 2000 and 2015 demonstrated high specificity for the detection of EPE (90%) and SVI (95%) [74]. However, sensitivity for these endpoints in the best performing series was 71–73%. Therefore, mpMRI may be limited in detecting microscopic EPE and SVI, which surely impacts the safety of nerve-sparing, especially in high risk patients.

Despite these limitations, there is level one evidence published by a single center in Norway suggesting that preoperative mpMRI does indeed reduce the rate of positive surgical margins at robotic radical prostatectomy and influences the rate of nerve-sparing in patients who otherwise might not have been considered for a nerve-sparing approach [75]. Among the n = 438 men randomized in this study to preoperative MRI vs. no MRI, sensitivity and specificity for detection of pT3 disease was 73 and 65%, respectively. The mpMRI information altered surgical approach in 27% of patients. Bilateral nerve sparing was performed 6.7% less frequently in the mpMRI group. The positive margin rate was reduced in the mpMRI group for cT1c patients (16% vs. 27%, $p = 0.035$). Among the patients found to have pT3 disease, 89% of them had only unilateral nerve sparing or no nerve sparing. This group did not have improvement

in positive margin rate with the mpMRI, however. Perhaps, even wider excision is required to render these patients free of positive margins, which has implications for post-operative potency. Further study is surely needed to clarify the role of mpMRI for pre-surgical planning.

### 5.2. Intraoperative nerve-sparing techniques

Refined understanding of the neuroanatomy of the cavernous nerves informs the surgical approach to and completeness of nerve-sparing. The endopelvic fascia is a multilayered sheath that encloses and buttresses the prostate and bladder and attaches these organs to the pubic bone via the puboprostatic ligaments. This fascia fuses as the arcus tendineus fascia pelvis just lateral to these organs. The fascial investments of the prostate may be further divided into the prostatic "capsule," periprostatic veins with their fascia, the lateral pelvic fascia (prostatic fascia), levator fascia, and levator ani muscles (**Figure 6**) [76]. Lepor and Walsh described nerve sparing in 1983, with the approach beginning at the prostate apex and proceeding in a retrograde fashion toward the prostatic vascular pedicle [6, 7]. In the modern era of minimally invasive and robotic techniques, the nerve-sparing is usually performed in an antegrade manner after first controlling the prostatic vascular pedicle. Initial experiences with robotic prostatectomy employed monopolar or bipolar electrocautery to control the pedicle until the detrimental role of thermal injury was fully appreciated.

Classical approaches to nerve-sparing have been described as "interfascial" vs. "intrafascial" techniques, as well as the "extra-fascial" approach when nerve-sparing is not performed (**Figure 7**). Interfascial dissection follows the plane lateral to the prostatic fascia, which may render the NVB prone to partial resection. The intrafascial technique follows the plane directly on the prostatic capsule, medial to the prostatic fascia and anterior to the Denonvilliers' fascia, especially at the 5:00 and 7:00 positions. Dissection is typically performed with both blunt and sharp dissection in an athermal manner to reduce transmission of heat and electricity to the proximal NVB.

Refinements in the understanding of the neuroanatomy have resulted in more sophisticated classifications of nerve-sparing. An important concept is the ability to perform incremental nerve sparing, not just as an "all-or-none" phenomenon. It has been suggested that optical magnification and the extended degree of freedom afforded by robotic surgery facilitates

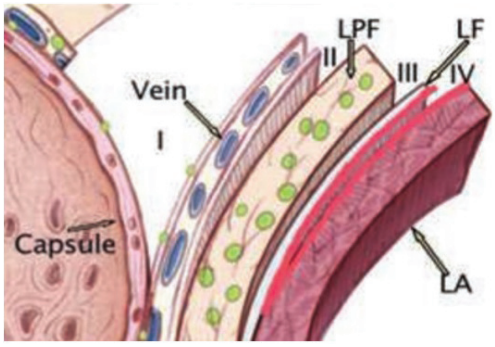


**Figure 6.** Planes for dissection of nerve-sparing based on prostatic fascial layers. LPF = lateral pelvic fascia (prostatic fascia); LF = levator fascia; LA = levator ani. Reprinted from Tewari et al. [76].

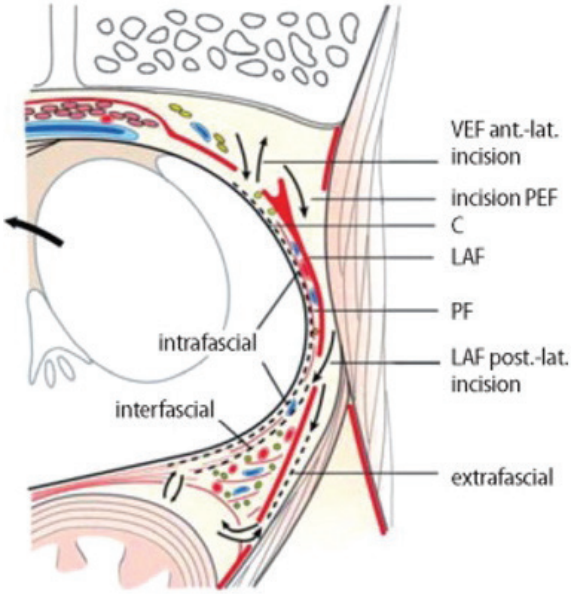


**Figure 7.** Intrafascial, Interfascial, Extrafascial dissection planes as the basis for nerve-sparing. VEF ant.-lat. = visceral endopelvic fascia anterior-lateral; PEF = parietal endopelvic fascia; C = capsule of prostate; LAF post.-lat. = levator ani fascia posterior-lateral; PF = prostatic fascia. Reprinted from Walz et al. [9].

development of dissection planes within the NVB itself to perform partial nerve sparing in the setting of concern for pT3 disease [12, 77]. This concept is illustrated in **Figure 6**. Dr. Tewari's series of n = 2317 patients was published in 2011 [76]. This approach relies on a risk-stratified approach to the "neural-hammock" as defined by the periprostatic veins and based on preoperative risk stratification based on Gleason score, PSA, digital rectal examination (DRE) findings, cancer volume, and mpMRI findings. The plane of dissection follows one of the grades illustrated in **Figure 6**. A similar grading system based on periprostatic arterial anatomy, rather than venous anatomy, has been proposed by Schatloff et al. (**Figure 8**). In their smaller series of n = 132 patients, they cite a landmark periprostatic artery to define grades as: 1, no nerve sparing; 2, <50% nerve-sparing; 3, 50% nerve sparing; 4, 75% nerve-sparing; 5, ≥95% nerve sparing [78]. The Menon et al. series reported on n = 2652 patients for whom nerve-sparing was initiated by incising the prostatic fascia anteriorly, termed "high anterior release" or the "Veil of Aphrodite" technique (**Figure 9**) [79]. The authors originally reported the development of a plane between the prostatic capsule and prostatic fascia cranially at the base of the seminal vesicles. This plane is propagated deep to the periprostatic venous sinuses with careful blunt and sharp dissection. For patients with significant periprostatic fibrosis after biopsy that impairs development of this plane, the authors recommend initiation of the dissection at the 2:00 or 10:00 position [79].

### 5.3. Outcomes of nerve-sparing techniques

Comparison of potency rates after the various surgical techniques is not straightforward, as there may be differences in patient demographics such as age and baseline potency,

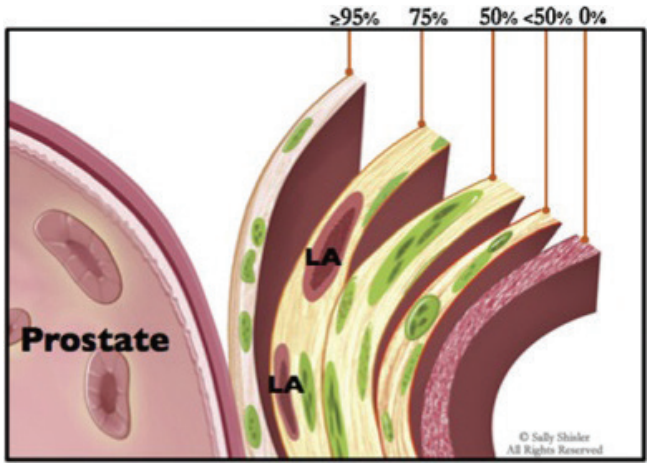


**Figure 8.** Grades of nerve-sparing based on anatomic landmark of periprostatic artery. LA = landmark artery. Reprinted from Schatloff et al. [78].

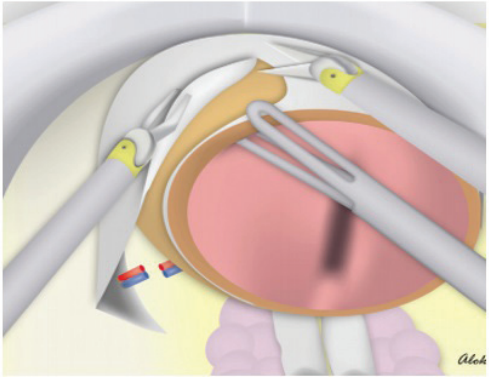

**Figure 9.** Plane of dissection for Veil of Aphrodite nerve-sparing technique. Reprinted from Menon et al. [79].

as well as tumor characteristics such as stage and grade that may influence the ability to perform bilateral nerve-sparing. Furthermore, based on the aforementioned variations in neuroanatomy among different patients, perfect execution of a given surgical technique may not be enough to accommodate a particular patient's anatomy, resulting in the variability of erectile function recovery. Definitions of potency also vary, with some studies reporting percentage return at a given time point or "return to baseline." The most robust series employ the validated questionnaires (IIEF, SHIM, EPIC), but precise cut-offs for restoration of function may vary. To add the possibility of subjective satisfaction beyond the numbers of the questionnaires, some studies also define potency as "erections suitable for intercourse" that are "satisfactory."

In the setting of these limitations, a recent systematic review and meta-analysis of six studies (only one randomized and three prospective; 4/6 minimally invasive approach) of n = 1663

patients reported improved erectile function at 6 months (RR 1.49) and 12 months (RR 1.40) for intrafascial vs. interfascial nerve-sparing.

Erectile function is not the only component of the Trifecta directly affected by nerve-sparing. Oncologic control with regard to the presence of positive surgical margins is also very important. Given the increased rates of biochemical recurrence and possibility of increased rates of metastasis and prostate-cancer specific mortality associated with the presence of a positive surgical margin, nerve-sparing outcomes must be understood within the context of margin status. Overall, the rates of PSM are around 15%, with rates ranging from 6 to 38% and influenced by pathologic stage, grade, and D'Amico risk category [80]. There have also been reports that bilateral vs. unilateral nerve-sparing in the setting of pT2 disease is associated with a higher rate of PSM, as demonstrated in a series of n = 9915 patients who underwent robotic prostatectomy at two institutions, with relative risk 1.52 [81]. Other studies have not corroborated an increased positive margin rate for intrafascial vs. interfascial nerve-sparing techniques (rate of 9% vs. 9.5%) [82]. The grades of nerve-sparing proposed by Dr. Tewari have been associated with excellent PSM rates, likely owing to preoperative risk stratification based on Gleason score, PSA, digital rectal examination (DRE) findings, cancer volume, and mpMRI findings. The rates of PSM for patients with nerve-sparing grades 1, 2, 3, and 4 were 9.9, 8.1, 7.2, and 8.7%, respectively ($p = 0.636$). The Schatloff series also reported their PSM rate, which was 9% overall. Although the rate of PSM for grade 1 NS was 0%, there was otherwise no consistent correlation between grade of NS and PSM rate (0, 5.7, 16.7, 7.5, 3.6% for grades 1, 2, 3, 4, and 5, respectively), perhaps reflecting good presurgical planning based on patient risk factors [78]. The Veil of Aphrodite technique by the Vattikuti Urology Institute reported a positive margin rate of 13%, which declined to 1.5% for pT2 disease after modification of approach to include en face oversewing of the DVC after apical transection [79].

Regarding the potency rates, it is necessary to standardize the definition of potency, which usually incorporates routine use of oral PDE 5 inhibitors. Furthermore, there is a distinction between restoration of penetrative sexual intercourse vs. return to baseline functioning. There are several contemporary series reporting erectile function outcomes after robotic prostatectomy. Tewari's risk-stratified approach to neural-hammock sparing in n = 2317 men resulted successful intercourse (score of ≥4 on question two of the SHIM and total SHIM >21) of 90.9, 81.4, 73.5, and 62% for nerve-sparing grades 1, 2, 3, and 4, respectively [76]. Regarding return to baseline function: grade 1, 81.7%; grade 2, 74.3%; grade 3, 66.1%; grade 4, 54.5%. Of note, this group also reported earlier return of continence associated with the higher grades of nerve-sparing, which has been controversial [83]. Incidentally, a recent systematic review and meta-analysis of 27 longitudinal cohort studies totaling n = 13,749 patients, however, reported that early urinary continence (at 6 months post-RP) was improved for patients undergoing nerve-sparing vs. non-nerve-sparing surgery (88.9% vs. 69.8%) [84].

Tewari's technical modification of adding real-time penile oxygen monitoring demonstrated that at 6 weeks postoperatively, a larger proportion of patients in the $O_2$ monitoring group had no ED (24.5% vs. 10.4%, $p < 0.05$) and at 52 weeks this difference was persistent (84% vs. 68%, $p < 0.05$). Furthermore, using the Sexual Health Inventory for Men (SHIM) validated questionnaire at 1 year, a greater number proportion of patients reported minimal to no ED (94% vs. 78%, $p < 0.05$). In this report, the authors did not sub-stratify by grade of nerve sparing [85] (see Section 5.4).

The Schatloff series on grade stratification based on periprostatic arterial anatomy did not report functional outcomes [78]. The Vattikuti Institute series included n = 1142 patients with minimum follow-up of 12 months and among men with normal preoperative function (i.e. SHIM >21) potency rates were 68% in the standard bilateral nerve-sparing patients and 93% in the bilateral Veil nerve-sparing patients [79]. Return to baseline rates depended on preoperative function, and for those without preoperative dysfunction, return to baseline was 39% for standard nerve-sparing and 73% for the Veil technique. Despite these very favorable results, the authors disclosed that only 50% of these patients attained normal SHIM score without medication. Although these findings suggest that the Veil offers improvements in recovery of erectile function, there may be a bias of surgeon experience, as the Veil technique was employed later in the learning curve of this single-surgeon series. This series also demonstrated 84% total urinary control, and 95% social continence (one pad or liner per day) at 12 months follow-up. The role of nerve-sparing in earlier recovery of continence has been corroborated by many series [86–88].

Some limitations of these studies are that they are single institution and often single-surgeon series and there is no direct comparison among different techniques to be able to assess superiority. Furthermore, there may be shortcomings with translation of these techniques into the larger urologic community compared to the immensely high-volume centers where these techniques were invented.

### 5.4. Intraoperative penile oxygen monitoring

The real-time impact of neurovascular bundle tension on cavernosal ischemia was investigated by Tewari et al. in n = 64 patients [85]. During robotic prostatectomy, these patients underwent real-time penile oxygen monitoring with the Odissey Tissue Oximeter probe placed 2 cm from the base of the penis. Surgical dissection was altered whenever the $O_2$ alarm sounded until oxygenation was restored to 85%. Functional outcomes were compared to a propensity-matched historical control group of n = 192 patients (matched for age, preoperative prostate specific antigen (PSA), baseline erectile function, comorbidity status, and extent of nerve-sparing). Steps in the operation associated with significant decline in tissue oxygenation included opening the endopelvic fascia, all of the nerve-sparing, excessive traction on the Foley catheter, seminal vesicles, or prostate during the apical dissection, and control of the dorsal vein complex (DVC) prior to apical dissection. Of note, control of the DVC if done after apical transection was not associated with significant penile ischemia. At 6 weeks postoperatively, a larger proportion of patients in the $O_2$ monitoring group had no ED (24.5% vs. 10.4%, $p < 0.05$) and at 52 weeks this difference was persistent (84% vs. 68%, $p < 0.05$). Furthermore, using the Sexual Health Inventory for Men (SHIM) validated questionnaire at 1 year, a greater number proportion of patients reported minimal to no ED (94% vs. 78%, $p < 0.05$). These findings provide clinical evidence for the importance of minimizing neurovascular bundle manipulation during robotic prostatectomy as a means of preventing neurapraxia/axonotmesis.

Similar evidence comes from a well-designed prospective, randomized, single-blinded study of n = 61 with normal preoperative erectile function from 6 centers [89]. Patients underwent robotic prostatectomy with traditional bilateral nerve sparing compared to nerve-sparing using the Cavermap Surgical Aid. A 12 months post-op, the Cavermap group had mean 15.9 minutes of greater than 60% nocturnal tumescence vs. 2.1 minutes as measured by the

RigiScan. The sexual function inventory questionnaire (SFIQ) scores at 12 months were not significantly different, however. Among those patients with intact response to nerve stimulation after nerve-sparing, 68% of those with bilateral response had recovery on SFIQ vs. 27% with unilateral response, and 0% with no response [89]. A subsequent multi-institutional study utilizing the Cavermap by five experienced surgeons demonstrated limited specificity to identify the precise location of the cavernous nerves, thus limiting its routine application during radical prostatectomy [90].

### 5.5. No countertraction technique

The detrimental impact of nerve traction injury may also be limited. A series emphasizing nerve-sparing with a lack of countertraction has been published (**Figure 10**). Kowalcyzk et al. reported statistical significantly different erectile function at 5 months post-robotic prostatectomy (24.9% vs. 18.4%, p = 0.004), which was confirmed in the multivariable regression model. These differences were no longer present at 12 months (34.7% vs. 33.5%, p = 0.849), independent of preoperative erectile function, laterality of nerve sparing, and inter- vs. intrafascial approach [91]. Therefore, "tractionless" surgery may accelerate functional return.

### 5.6. Minimizing use of electrocautery/thermal energy

In the early experience of robotic prostatectomy, many centers performed dissection of the neurovascular bundle with electrocautery. Ahlering et al. demonstrated slower return of erection function as measured by the IIEF-5 and two questions on the EPIC questionnaire. Of the n = 125 patients, only 36 met their inclusion criteria, (age < 66 and IIEF-5 score 22–25), with n = 3 having had monopolar electrocautery and n = 33 having had bipolar cautery. Of note men with Gleason 7–10 and high volume disease had ipsilateral wide excision of the NVB. Although there was no comparison group, erectile function recovery was modest especially when compared to modern historical series. Among those who had bilateral nerve-sparing, recovery at 15 months was 44.4% and at 24 months was 67.9% [31]. These findings help to support the clinical principle of avoidance of thermal energy during dissection of the neurovascular bundle.

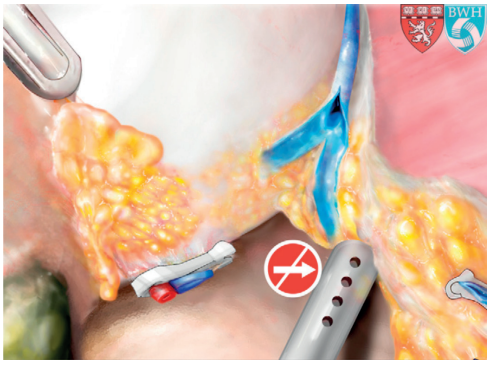


**Figure 10.** Technique of nerve-sparing with assistant suction neurovascular bundle countertraction which is avoided in the Kowalcyzk et al. technique of nerve-sparing. Reprinted from Kowalczyk et al. [91].

### 5.7. Seminal vesicle preservation

Building on several observational studies [92, 93], Gilbert et al. reported a randomized controlled, Phase II trial of n = 140 men who underwent radical prostatectomy [94]. Seminal vesicle-sparing approach was employed in 71 men. At 6 and 12 months post-operatively, sexual and urinary function scores were similar on the EPIC questionnaire (erections firm enough for intercourse in 67.7% vs. 56.3%, p = 1). In addition, positive surgical margin status and 12-month biochemical recurrence rates were similar. This approach has understandably not been widely adopted.

### 5.8. Hypothermic robotic radical prostatectomy

Finley et al. reported the potential benefit of regional hypothermia/cold dissection of the neurovascular bundle in a case–control study of n = 115 who underwent robotic prostatectomy [95, 96]. The rationale for the endeavor mirrors developments in neurosurgery and cardiac surgery that have established significant benefits in randomized studies. Hypothermia was employed to minimize iatrogenic tissue inflammation and consequent cellular edema, lactic acidosis, nerve conduction blockade, free radical damage, and apoptosis that characterizes damage to muscle and nervous tissue. Cold intracorporeal irrigation was employed along with an endorectal cooling balloon cycled with saline at 4°C. Potency rates at 12-months were favorable. Patients subjected to hypothermia were compared to a historical cohort of n = 667 patients. Temperature probes monitored the endorectal and intracorporeal temperatures, which declined to mean 18.7 and 25.6°C, respectively. Potency was assessed during validated questionnaires and defined as "erections adequate for penetration" and "were the erections satisfactory." Potency at 3 months was similar, but at 15 months, the hypothermic group had significantly better function (83% vs. 66%, p = 0.045). There were no differences in oncologic outcomes and no complications related to the technology [97]. These results need further multi-institutional investigation.

### 5.9. Clipless antegrade nerve preservation

Rather than perform the nerve-sparing in the conventional antegrade (base to apex) fashion, some centers have described a medial to lateral approach. After division of the posterior bladder neck, the posterior plane along the prostate is developed toward the prostatic apex in the midline. The dissection proceeded laterally to release the vascular pedicles and neurovascular bundles in a medial to lateral direction, with sparing use of bipolar cautery. No monopolar cautery or clips were used. Chien et al. reported their series of n = 56 patients who underwent robotic prostatectomy using this approach between 2003 and 2004 [97]. Their outcome metrics relied on the Rand Medical Outcomes Study 36-Item Health Survey, version 2, as well as the University of California, Los Angeles, Prostate Cancer Index up to 12 months postop. Return to baseline potency (allowed use of oral phosphodiesterase inhibitors) among patients with bilateral nerve-sparing occurred in 69%. The positive surgical margin rate in this series was similar to other published techniques at 10.7% [97].

### 5.10. Intraoperative frozen section analysis

There have been multiple reports of the utility of intraoperative frozen section to allow for more aggressive nerve-sparing in patients whose risk factors may have otherwise prompted

a non-nerve sparing surgical approach. In an open series of n = 608 patients who underwent RP, 83 patients were found to have a palpable lesion close to the prostatic capsule [98]. A 4 cm wedge of tissue was excised in the suspicious area for intraoperative frozen section (IOFS). A total of 93% of these IOFS were positive for carcinoma, and 36% of these were pT3. Final positive margin rate overall was 16%. This real-time decision-making allowed for ipsilateral nerve-sparing in 52% of the cases without a negative impact on PSM. Of note, there was a false positive PSM rate of 17%. The applicability to the modern era of robotic prostatectomy may not be lost, but would be based on gross visual suspicion of tumor violation during nerve-sparing.

Another center has pioneered the Neurovascular Structure-Adjacent Frozen-section Examination ("NeuroSAFE") approach to nerve sparing [99]. In this technique, a bilateral nerve-sparing procedure is performed and then the prostate gland is promptly extracted from the surgical field and whole gland circumferential frozen section analysis is performed. The original series consisted of n = 11,069 who underwent open RRP from 2002 to 2011, n = 5392 of whom had the NeuroSAFE technique. When a margin was found to be positive, the ipsilateral neurovascular bundle was resected, including the rectolateral component of the Denonvilliers' fascia, prior to the vesicourethral anastomosis. The sensitivity and specificity of this approach was 93.5 and 98.8%, respectively, with accuracy of 97.3%. Of the 25% found to have PSM initially, 85% of these were converted to final negative margin. False negatives occurred in 2.5% and all of these margins were < 0.5 mm. There were significant reductions in PSM rates within each pathologic tumor stage (except for pT3b) and an increase in the rate of nerve-sparing for all stages. Of note processing time took about 35 minutes and there was no delay in surgery, as hemostasis, bladder closure, lymph node dissection, and posterior reconstruction could be performed during this time (**Figure 11**) [99].

This technique has been translated into robotic surgery in n = 1570 patients from 2004 to 2012, in whom n = 1178 had the NeuroSAFE technique. Intraoperative blood loss was equivalent and nerve-sparing rate increased significantly (overall 97% vs. 81%; pT2 99% vs. 90%; pT3a 94% vs. 74%; pT3b 91% vs. 30%). Furthermore, rate of PSM improved with NeuroSAFE (overall 16% vs. 24%; pT2 8% vs. 15%; pT3a 22% vs. 39%; pT3b 49% vs. 67%; $p < 0.05$) [100]. These findings have contributed to the development of the "Safe-R score," a composite measure of margin status and laterality of nerve sparing [101].

### 5.11. The influence of surgical modality on nerve-sparing success

It has been postulated that the loss of haptic feedback renders traction-free nerve-sparing difficult during robotic prostatectomy. Conversely, the optical magnification and seven-degrees of freedom afforded by robotic surgery may allow for superior delineation of the neuroanatomy, precision of dissection, and even performance of partial or incremental nerve sparing for patients with concern for locally advanced disease. Such patients may have otherwise been subjected to a non-nerve-sparing technique. Tewari et al. reported earlier return of 50% erectile function (as reported on the EPIC questionnaire) after robotic prostatectomy vs. RRP (mean 180 days vs. 440 days, $p < 0.05$) and earlier return to intercourse (340 days vs. >700 days, $p < 0.05$) Interestingly, these findings were shown even in the setting of a greater number of patients post-RRP using sildenafil (65% vs. 42%) [102]. Such findings were also corroborated by a prospective, non-randomized trial of robotic prostatectomy vs. RRP in n = 208 patients from 2006 to 2007. At

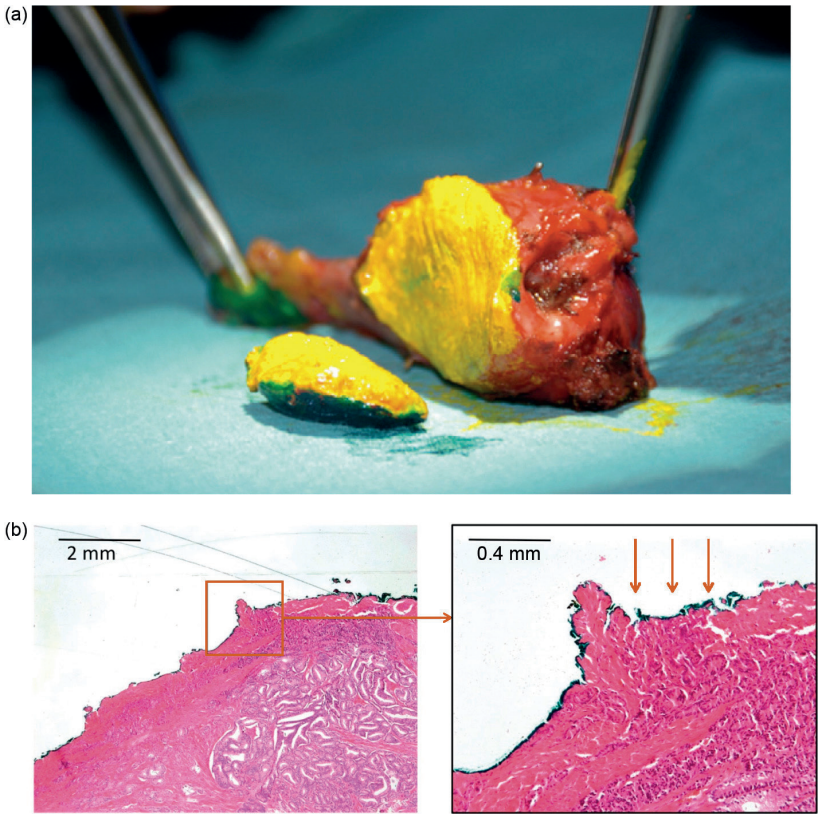


**Figure 11.** A. Intraoperative picture of NeuroSAFE technique. B. Intraoperative frozen section with tumor contact at linked surface. Reprinted from Beyer et al. [100].

12 months follow-up, of the patients with bilateral nerve-sparing, those who underwent the robotic procedure had superior recovery of erectile function on the IIEF-5 questionnaire (81% vs. 49%, $p < 0.001$) [62]. Further contemporary evidence comes from a systematic review and meta-analysis of 31 studies published between 2008 and 2011 totaling n = 3491 patients [63]. Outcome measures of erectile function were heterogeneous, with some studies employing SHIM > 21 and others using "erections sufficient for intercourse." Cumulative analyses of the six studies with suitable follow-up demonstrated better 12-month potency rates after robotic surgery vs. RRP (24.2% vs. 47.8%; odds ratio 2.84, $p = 0.002$). Absolute risk reduction was 23.6%. Furthermore, 24-month potency was 84% vs. 47% (odds ratio 6.01; $p < 0.001$) Comparison between robotic and laparoscopic approaches was not significant (39.8% vs. 55.6%, $p = 0.21$).

These comparisons may be hampered by different definitions and metrics for erectile dysfunction, patient selection for surgery, and variations in post-operative penile rehabilitation at different institutions. Further evidence is forthcoming from the first randomized controlled phase 3 study of robotic vs. open prostatectomy conducted by Yaxley et al. out of Australia [103]. Although the study randomized n = 326 men and plans to report on urinary

and sexual function outcomes (via the EPIC and IIEF questionnaires) at 6 and 12 weeks, as well as 24 months, published results are immature at 12 weeks only. There were no significantly different urinary or sexual function scores at 6 and 12 weeks, nor were there differences in health reported quality of life.

A counterargument to the benefits afford by robotic surgery, however, states that more aggressive nerve sparing, although technically feasible, may not be oncologically safe, given the risk of positive margins. Indeed, the Preston et al. study revealed that positive margins were more likely in patients treated with robotic surgery (relative risk 1.76) compared to open surgery, while there was no difference between lap and robotic surgery [81]. These findings were not corroborated in a very large, albeit retrospective, multi-institutional, multi-national study of n = 22,393 patients, however, which found the lowest rate of positive margins in robotic prostatectomy (13.8%) vs. laparoscopic (16.3%) vs. open (22.8%) [104]. A recent systematic review and meta-analysis by Novara et al. of 21 studies totaling n = 19,238 patients reported similar PSM rates among robotic, laparoscopic, and open surgery, both overall and when sub-stratified into pT2 patients (mean 15%, range 6.5–32% [105]. More recent evidence to mitigate this controversy comes from the previously referenced randomized Phase 3 trial of open vs. robotic prostatectomy by Yaxley et al. Oncologic outcome were equivalent between the two groups, including PSM overall, and for pT2 and pT3 patients (15% vs. 10%, 3% vs. 2%, 11% vs. 8%, respectively) [103].

One notable difference between the open and robotic approach is the use of a retrograde vs. antegrade approach to the dissection of the neurovascular bundle. There is a theoretically reduced risk of placing a clip across the neurovascular bundle with the retrograde approach, which releases the bundle from the prostate prior to obtaining vascular control [106]. These different approaches were compared in a propensity-matched series of n = 344 patients undergoing robotic prostatectomy. Using validated questionnaires at 3,6, and 9 months, the potency rate was significantly higher after the retrograde approach (92.9% vs. 72.1% at 9 months), and this finding was maintained with multivariable analysis. Of note, the PSM rate was similar between groups (11.6% vs. 7%, $p > 0.05$) [107]. Of note, this was a single-surgeon series and the approaches were performed in an interfascial manner, which may not reflect the most current understanding of the cavernous neuroanatomy. Also, the retrograde approach was generally performed more recently in the series with possible artifactual enhancement in outcome from being later in the learning curve. Furthermore, the seemingly excellent results from either approach in this series are likely a consequence of the permissive definition of erection function (erections firm enough for penetration in >50% of attempts).

Of note, although intriguing to consider if there are any technical advantages to nerve sparing with an extraperitoneal vs. transperitoneal approach to robotic prostatectomy, the extant literature has thus far focused exclusively on perioperative rather than functional outcomes [108, 109].

## 6. Penile rehabilitation

Several options for penile rehabilitation have been proposed and investigated, including pharmacotherapy with oral phosphodiesterase inhibitors or penile intracavernosal injection, as well as use of a vacuum erection device and penile constrictive ring. Often a multimodality

approach is advocated. Compliance with these recommendations depends on myriad factors, including physician counseling, patient motivation, and even socioeconomic status—as many of the therapies are not covered under health insurance. The PCOS trial reported that 43% of men tried sildenafil, 25% tried a vacuum erection device, and 17% tried intracavernous injections [52]. Admittedly, the denominator of men who were actually offered these treatments is not known.

The rationale for these treatments has been investigated in preclinical models. There is indeed precedent for treatment success in animal models of chronic low-dose tadalafil administration, with increased cavernosal smooth muscle, decreased fibrous tissue, and functional enhancement of erectile function [110–112]. Similar findings have been reported for sildenafil after bilateral cavernosal nerve damage in a rat model. Nerve damage resulted in elevation in several pro-inflammatory cytokines (interleukin-1β, transforming growth factor β) and markers of oxidative stress (nicotinamide adenine dinucleotide phosphate [NADPH] oxidase, myeloperoxidase, inducible nitric oxide synthase, tumor necrosis factor receptor superfamily member 5 [CD40]), which then normalized after administration of sildenafil in the drinking water. Levels were measured by polymerase chain reaction (PCR) and proteome expression of pelvic ganglia neurons [113].

### 6.1. Mechanotherapy

The vacuum erection device often in conjunction with penile constrictive ring are routinely recommended for use to assist with recovery of potency after radical prostatectomy. This therapy not only allows for tumescence and penetration, but also cavernosal sinus expansion, smooth muscle "stretching," and mitigation of hypoxia when used on a regular basis [114, 115]. Compared to pharmacotherapies—which are often not covered by the patient's health insurance—VED may be more cost-effective, with a decreased side effect profile and the opportunity for the patient and his partner to take an active role in convalescence. In addition, the mechanism of action does not require intact cavernous nerves for success. There have been multiple retrospective studies examining the impact of the VED [115–117]. These suggest improvement in return of spontaneous erections. In particular, a retrospective study of n = 203 patients who underwent robotic radical prostatectomy between 2007 and 2011 investigated whether PD5I alone, VED alone, or a combination of the two yielded the highest improvement of the SHIM questionnaire, substratified into three groups of baseline EF (SHIM 8–16, SHIM 17–21, SHIM 22–25). For each of the baseline EF groups the combination therapy resulted in the highest proportion of successful potency (erections suitable for penetration) and with the shortest latency period [118].

Randomized evidence comes from Raina et al., who reported on n = 109 patient who underwent open RP (both NS and non-NS) randomized post-op to daily VED therapy vs. observation. Compliance with the device was 80% with 55% partner satisfaction rate. After 9 months of treatment IIEF-5 score was significantly increased for both the NS and non-NS patients compared to the no treatment group. Furthermore, decreased penile length was reported in 63% of the control group vs. 23% among patients who responded to VED treatment [115].

Regarding timing of therapy, earlier initiation of 10 minutes daily VED therapy (1 month post-op vs. at 6 months) has been shown in a small randomized trial of n = 28 men to be

superior in terms of 1. IIEF score at 3- and 6-months, and 2. preservation of stretched penile length (vs. 2 cm mean decrease observed in the delayed therapy group) [119].

### 6.2. Pharmacotherapy

The majority of penile rehabilitation studies incorporate early post-op therapy. Phosphodiesterase type 5 inhibitors have been demonstrated to be effective for the treatment of erectile dysfunction through their inhibitory effect on the enzyme that degrades cGMP. These medications augment the nitric oxide-mediation erectile response through increased relaxation of the cavernosal sinus smooth muscle [120]. The commercially available medications have different half-lives of activity, with Tadalafil being the longest ($T_{1/2}$ sildenafil 3–5 mg; vardenafil 4–5 hours; tadalafil 17.5 hours) [121]. There is also experience with both intraurethral and intracavernosal prostaglandin E, which act via a cAMP-related mechanism to effect cavernosal smooth muscle dilatation [122]. Montorsi et al. published the first randomized, placebo controlled trial in 1997, involving intracavernosal injection of alprostadil three times per week × 12 weeks beginning 1 month after open RP [23]. Newer formulations of intracavernosal therapy include Trimix (prostaglandin, phentolamine—a non-selective alpha-blocker—and papaverine—a non-selective PDE5 inhibitor—and Bimix (papaverine and phentolamine). Given the invasive nature of ICI—as well as the putative higher complication rate regarding pain, hematoma, penile plaque formation, and priapism—this therapy is not universally accepted by patients. Therefore, there is much interest in the oral PDE5 inhibitors as a mechanism of increasing intracavernosal cGMP to promote smooth muscle relaxation and mitigate of the post-RP hypoxic state.

#### *6.2.1. Oral PDE 5 inhibitors*

There have been several prospective, randomized studies in this domain, which are summarized **Table 1**. Rationale for these trials was based on findings that daily sildenafil preserves intracorporeal smooth muscle after radical retropubic prostatectomy [123]. The studies tended to exclude men with high grade prostate cancer (i.e. Gleason 8) and those who required adjuvant radiation therapy. Latency of medication initiation is also variable, ranging from time of catheter removal to 4 weeks post op. Based on the cavernous neurotomy rat models in which post-injury cavernous smooth muscle apoptosis begins in 1 day and peaks at 1 week, earlier initiation of treatment has definite clinical rationale [34]. Furthermore, the study end-points are not identical. Some examine the impact on erections during an active treatment phase and others examine the rate of return of spontaneous erections (that is, without the need for pharmacotherapy). The proportion of open vs. robotic RP are also variable (open RP: 39.7–100%). The Jo et al. study out of South Korea is the only study comprised exclusively of patients who underwent robotic prostatectomy, and showed more complete return of erectile function at 12 months with immediate post-catheter removal initiation of 100 mg sildenafil twice weekly compared to waiting until 3 months after surgery [124]. The concomitant use of VED in these studies is not clear, which adds another limitation to their interpretation. Also of interest is a follow-up study to the study by Pavlovich et al. [172] suggesting poorer EPIC scores with nightly sildenafil 50 mg compared to PRN dosing, largely in the urinary irritative and bother subscales of the questionnaire [125]. Further study is required to clarify the implications of this report.

| Author | Patients | Study drug | Study schema | F/U | Outcome metric | Findings | Conclusion | Limitations |
|---|---|---|---|---|---|---|---|---|
| Montorsi et al. [23] | 30; mean age 62, "reported satisfactory intercourse preop;" bilateral nerve-sparing | Alprostadil TIW × 12 weeks | Dose titrated for efficacy (2–14 μg) vs. no injection | 3 months | "Recovery of spontaneous erections" | 80% compliance with injections;<br>67% recovery vs. 20% | Early ICI with alprostadil increases recovery of spontaneous erections | No sham injection group; no IIEF standardized questionnaire; waited 1 month short f/u; 17% complication |
| Montorsi et al. [110] | 445 (18–64 years); IIEF-EF ≥ 26; bilateral NS; mean age 57.1 | Vardenafil × 9 months | 10 mg nightly vs. 10 mg PRN within 2 weeks postop | 12 months | IIEF-EF ≥ 22 after 2-month washout; then open label PRN | Double blind period: IIEF > 22: 24.8, 32, 48.2% (placebo, nightly, on demand);<br>After 2 months washout and open label PRN no difference | On demand dosing is effective | Did not limit frequency of on demand dosing; dose up to 20 mg |
| Padma-Nathan et al. [171] | 76 (18–70 years) s/p RRP; 8 on Q3 and Q4 of IIEF; mean age 55.5 | Sildenafil × 9 months | Nightly 50 mg, 100 mg, placebo within 4 weeks | 12 months | IIEF after 8 week washout; plethysmography | IIEF Q3 + Q4 ≥8 and "satisfactory": 4, 26, 29% (placebo, 50 mg, 100 mg) | Sildenafil improved erectile function, but no dose dependence | Closed early for lack of treatment effect; very low rate of EF in placebo arm; waited 4 weeks |
| Pavlovich et al. [172] | 100 (<65 years) s/p MIS RP; IIEF-EF ≥ 26, uni-/bilateral NS; mean age 53.9 | Sildenafil × 12 months | 50 mg nightly vs. PRN (max 6 per month) immediately after RP | 13 months | IIEF, EPIC after 1-mo washout | IIEF-EF > 21: 33.2, 50% (nightly, on demand) | No difference in nightly vs. on demand | No pure placebo arm |
| Montorsi et al. [173] | 423 (≤68 years; IIEF-EF ≥ 22; PSA <10 ng/mL; GS < 8. Bilateral NS; mean age 57.9 years | Tadalafil × 9 months | 5 mg daily vs. 20 mg PRN; 6 week washout, then 3 months open-label 5 mg daily | 13.5 months | IIEF-EF ≥ 22 after 6-week washout; penile length loss | 20.9, 16.9, 19.1% IIEF-EF ≥ 22 (daily, on demand, placebo) after washout—non-signif; 5 mg daily better IIEF-EF vs. placebo | "Unassisted EF was not improved after cessation of active therapy for 9 month."<br>Reduced penile length loss in 5 mg daily (difference 4 mm) | Binary definition of success limited power; patients with mild ED (IIEF-EF 22–25) were included |

| Author | Patients | Study drug | Study schema | F/U | Outcome metric | Findings | Conclusion | Limitations |
|---|---|---|---|---|---|---|---|---|
| Canat et al. [174] | 129; mean age 63 years; IIEF-6 no or mild ED; bilateral NS | Tadalafil × 12 weeks | 20 mg TIW vs. 20 mg PRN vs. placebo at time of catheter removal | 6 weeks, 12 months | IIEF-6 score at 6 weeks and 12 months | 6 weeks no diff; 12 months, higher IIEF for TIW group (19.9 vs 15.8 vs. 13.47; TIW, PRN, none) | 20 mg TIW is effective and well-tolerated | Lack of placebo |
| Kim et al. [175] | 97; SHIM ≥ 21 and RigiScan >60% × 10 minutes nocturnal erection; b/l NS (robo-, open); mean age 54 years | Sildenafil × 12 months | 50 mg starting night after surgery vs. placebo; all patients received 6 tabs × 100 mg/months PRN | 13 months | IIEF; RigiScan | RigiScan 40% potency at 13 months for both groups; IIEF > 21 29% vs. 32.4%, non-significant | No difference for 50 mg nightly sildenafil vs. 100 mg PRN | 76% compliance; under accrual; lack of true placebo arm |
| Jo et al. [124] | 120; >50 years; IIEF-5 ≥ 17; NS-eligible but not always performed; s/p RALP (~82%);mean age 63.7 years | Sildenafil × 12 months | Sildenafil 100 mg 2×/ week after catheter removal × 3 months; delayed group started at 3 months post-op; then PRN 12 months therapy | 12 months | IIEF ≥ 12 months | IIEF ≥ in 41.4% vs. 17.7% (early vs. late); PRN usage similar between groups | Early sildenafil improved full EF recovery during 12 months post-RP | Early group younger (61.7 vs. 65.6); small study |

TIW = three times per week; RCT = randomized controlled trial; ICI = intracavernosal injection; f/u = follow-up; NS = nerve sparing; IIEF = International Index of Erectile Function; EF = erectile function; PRN = pro re nata ("on demand"); RRP = radical retropubic prostatectomy; MIS = minimally invasive surgery; RP = radical prostatectomy; EPIC = Expanded prostate cancer index composite; EF = Erectile function; PSA = prostate specific antigen; REF = Residual Erection Function; RALP = robotic-assisted laparoscopic prostatectomy.

**Table 1.** Randomized controlled trials of post-prostatectomy pharmacologic penile rehabilitation.

A majority of these trials for ED after radical prostatectomy examine daily vs. on-demand dosing schedules. Of note, a randomized, double-blind trial (RESTORE study) in men with mild to moderate ED (IIEF-EF 15–20; *not post-prostatectomy*) of 10 mg vardenafil daily vs. PRN showed no differences in increase of IIEF-EF score [126]. Similar findings appear to be borne out in the post-RP series as well (*see below*). Side effect profiles of the treatment groups were largely favorable and usually without the need for drug discontinuation. Furthermore, daily vs. on demand schedules did not have significantly different adverse effects in a recent meta-analysis, and absolute rates of side effects were not substantially different between treatment and placebo groups overall (59.6% vs. 48.4%) [127]. Side effects generally reported included headache, flushing, dyspepsia, and rhinitis, none of which are severe.

#### *6.2.2. Intraurethral prostaglandin*

Intraurethral alprostadil (Medicated Urethral System for Erection, *MUSE*™) has also been developed for use in erectile dysfunction. Experience with this drug for non-post-RP erectile dysfunction has been limited by lack of efficacy and penile pain/dysuria in a large number of patients. Early experience with MUSE after 6 months of post-RP ED showed 55% of the n = 54 patients able to achieve erections suitable for penetration, although only 48% continued long-term therapy (57% of men discontinued therapy for inefficacy) [128]. The author's experience with application of the therapy at 3 weeks post-op for a duration of 6 months showed erections firm enough for penetration in 74% of patients compliant with treatment. All patients reported mild penile pain or urethral burning and 32% of patients discontinued treatment [129].

### 6.3. Pelvic floor PT

The role of pelvic floor physical therapy (PFMT; "Kegel" exercises) on return of urinary continence has been well understood, as evidenced by meta-analyses demonstrating earlier return of continence with preoperative PMFT and biofeedback [130, 131]. The impact of such therapy on recovery of sexual function has also been explored. Physical therapy efforts focus on the bulbocavernosus (bulbospongiosus) and ischiocavernosus muscles. Contraction of the ischiocavernosus muscle may compress the proximal aspects of the corpora cavernosa and increase intracavernosal pressure during erection [132]. Also, muscle contraction has been shown to increase levels of brain-derived neurotrophic factor in muscle cells, which may have a role in promoting neuronal growth after nerve injury [133]. A trial of n = 55 men with ED for ≥6 months randomized one group to PFMT with biofeedback + lifestyle changes vs. lifestyle changes alone [134]. Lifestyle changes consisted of alcohol intake reduction, smoking cessation, increasing exercise, and avoiding bicycle riding. Outcomes were assessed with IIEF and anal pressure measurements. At 3 months follow-up, the PFMT group had greater improvement in IIEF than the lifestyle changes alone group ($p < 0.001$). Other concomitant therapies for ED (i.e. PDE5 inhibitors or vacuum erection device) were not disclosed by the authors, limiting the strength of the results. Also, there were no post-prostatectomy patients in this cohort.

With regard to prostatectomy, the timing is such physical therapy is also interesting to consider and there is no established consensus of whether pre- and postoperative physical therapy is superior to postoperative therapy alone. Perez et al. examined the use of biofeedback

preoperatively to strengthen the levator muscles prior to radical prostatectomy [135]. Their methods employed a device that provided visual feedback based on intra-anal pressures. In this prospective cohort study, a total of n = 20 patients completed 10 sessions pre-RP and n = 32 patients proceeded directly to surgery. Potency outcomes were assessed using the IIEF-5, although follow-up time was not clear. The erectile dysfunction rate in the physical therapy group was 5% vs. 48.6% in the control group $< p < 0.001$). There are likely variations in physical therapy technique and not all methods are standardized.

The impact of PFMT on erectile function after radical prostatectomy has also been examined. Prota et al. studied n = 52 patients who underwent open RP and randomized them to PFMT + biofeedback weekly × 3 months (beginning at time of catheter removal) vs. verbal instructions only [136]. Nerve-sparing was performed in a similar proportion of patients in each group (64.7% vs. 68.8%). There was earlier recovery (IIEF >20) in the treatment group which persisted at 12 months post-op (47.1% vs. 12.5%). The authors report an absolute risk reduction of 34.6%, with number needed to treat (NNT) of 3. These results are even more encouraging given that oral PDE5 inhibitor therapy was withheld during the study. This study provides level 1b evidence supporting the use of post-operative PFMT for erectile function recovery [136]. Optimal schedule and intensity has yet to be determined.

Additional randomized controlled trials are needed to further assess the utility of PFMT in the restoration of potency.

### 6.4. Novel therapies

#### *6.4.1. Hyperbaric oxygen*

The role of hyperbaric oxygen (HBO) in Urology for treatment of radiation-induced hemorrhagic cystitis is well known. Application of this technology to post-RP erectile dysfunction is controversial. There have been preclinical studies in rats with cavernous nerve injury undergoing HBO that demonstrate higher intracavernosal pressure/mean arterial pressure ratio, increased levels of penile nerve growth factor (NGF) and endothelial nitric oxide synthase (eNOS) compared to the controls. Tissue studies on smooth muscle to collagen ratio, however, did not show a significant difference after HBO [137]. Exposure to 100% oxygen at 2 atm pressure induces stem cell differentiation and neovascularization, as well as vasoconstriction that attenuates tissue edema [138]. These findings underlie the rationale for translational studies. Chiles et al. published the first randomized, double-blind controlled trial of HBO vs. air for men after RP [139]. Although the authors were unable to demonstrate significant difference in IIEF score at 18 months, uncertainty about the proper regimen for therapy (total number and frequency of treatments) and lack of a true "sham" group may have limited their ability to detect a clinically relevant difference in outcome.

#### *6.4.2. Neuroprotective agents*

There is a growing body of literature on drug therapy to preempt or mitigate the post-cavernosal nerve injury pro-inflammatory environment. The immunophilin ligand FK506 (tacrolimus)—traditionally thought of as an immunosuppressive agent and widely used in

for solid organ transplant—has been implicated in a neuroprotective role when administered as early as 1 day following partial nerve-crush injury in a rat model [140]. Further work has demonstrated improved intracavernous pressure/mean arterial pressure ratio, restoration of inducible nitric oxide synthase (iNOS) staining, reduced apoptosis, preservation of cavernosal architecture, and upregulation of glutathione peroxidase (GPX) with resultant decrease in oxidative-stress-induced tissue damage [141, 142].

Pioglitazone, a thiazolidinedione used for the treatment of diabetes mellitus, may enhance neuronal survival and regeneration and decrease inflammation, and has been shown to be neuroprotective in models of sciatic nerve ischemia and optic nerve crush injury, as well as BCNI [143–145]. Furthermore, a small randomized controlled trial has shown efficacy of this agent for erectile dysfunction refractory to sildenafil [146]. A study by Katz et al. investigated the impact of pioglitazone on pelvic ganglion neurons after bilateral cavernosal nerve injury (BCNI) in Sprague-Dawley rats [147]. Four groups were examined: sham surgery, BCNI, BCNI + post-operative pioglitazone, BCNI + pre- and post-operative therapy. Gene expression profiles of neuronal nitric oxide synthase, neurturin, glial cell line-derived neurotrophic factor family receptor alpha-2 (GFR$\alpha$2), and $\beta$-III tubulin were upregulated in the pre-operative therapy group [147]. Further work is necessary to fully explore the utility of this therapy.

*6.4.3. Amnion-chorion membrane*

Dehydrated human amnion-chorion membrane allograft (dHACM) is a source of implantable neurotrophic factors and cytokines which promote neural survival and facilitate axonal regeneration. Its application has been examined in a rat model of axonal regeneration after spinal cord injury [148]. Clinically, it has been applied in the treatment of burns, corneal injuries, chronic venous ulcers, and chronic wounds [149]. There has been preliminary work in the placement of this membrane after bilateral nerve-sparing robotic RP to accelerate erectile functional recovery after surgery [150]. A single-surgeon propensity-matched analysis of preoperatively potent (SHIM >19) and continent (American Urological Association Symptom Score < 10) patients (n = 58) demonstrated earlier return of continence (1.2 months vs. 1.8 months, p = 0.033) and potency (1.34 months vs. 3.39 months, p = 0.007) with the wrap. (AmnioFix; *MiMedx Group, Marietta, GA, USA*) Some limitations of this series include the small size, lack of randomization, and short mean follow-up of 4 months, which limits conclusions about oncologic safety vis-à-vis risk of biochemical recurrence (BCR). Furthermore, functional recovery rates appear much higher than other series in the literature, and may be a consequence of the recall bias used to assess level of function. These preliminary results are certainly encouraging.

The dHACM allograft wrap was recently examined in a series of n = 940 patients (preoperative SHIM > 20) who underwent robotic RP with bilateral nerve-sparing [151]. A total of n = 235 had bilateral dHACM placement and these were propensity matched in a 1:3 proportion to non-dHACM patients (n = 705). Potency recovery rates were higher in the dHACM group at all time points except 12 months. Time to potency was significantly shorter in the dHACM group after bilateral NS (2.2 months vs. 2.8 months, p = 0.029) and partial NS (3 months vs. 3.9 months). After 12 months follow-up, erections sufficient for penetration were similar. Of note,

the recovery rates in this study were higher than what is generally reported in the literature. Also, although the rate of biochemical recurrence at 12 months was similar between groups, longer follow-up is certainly needed to demonstrate the oncologic safety of this application of technology.

A recent pre-clinical study of the role of hemostatic tissue sealing sheets has also investigated the impact on erectile function recovery in a series of 21 Sprague-Dawley rats [152]. The TachoSil (CSL Behring, Tokyo, Japan) is a collagen sponge coated on one side with fibrinogen and thrombin and is approved for achieving hemostasis during surgery. Contact between the sheet and blood or serosanguinous fluid results in deposition of a fibrin clot. Compared to sham surgery, the rats who underwent cavernous nerve dissection and had the TachoSil placed demonstrated similar intracavernous pressure/mean arterial pressure ratios at 4 weeks post-op. Furthermore, PCR-measured expression of inflammatory and oxidative markers (internleukin-6, tumor growth factor beta1, and heme-oxygenase-1) in the major pelvic ganglion was significantly reduced in the sheet group ($p < 0.05$).

*6.4.4. Stem cell therapy*

Stem cells may be harvested from growing embryos (embryonic stem cells) or as allografts from bone marrow or adipose tissue (mesenchymal stem cells). This technology has been applied to rat models of bilateral cavernosal nerve crush injury and shown considerable promise. Bochinski et al. [153] conducted a study of embryonic stem cells induced along the neuronal cell line with brain-derived neurotrophic factor [153]. These stem cells were then injected into the major pelvic ganglion (MPG) (group 3) and into the corpora cavernosa (group 4) of rats after BCNI. The study was well controlled with sham surgery (group 1) as well as a BCNI group with injection of culture media only (group 2). Volume of stem cells injected was 500 μL of a 10,000 cells/mL solution. Erectile response was assessed by electrostimulation of the cavernosal nerve at 3 months. Immunohistochemistry was also performed of the penile tissue to assess levels of nitric-oxide synthase-containing fibers and neurofilament concentration. Intracavernosal pressure in response to electrostimulation was greatest for sham surgery and lowest for group 2, which was also significantly lower than groups 3 and 4. The neurofilament stain of tissue taken from the MPG and the corpus cavernosum was also greater in groups 3 and 4 compared to group 2 (**Figure 12**). Such neurofilaments are involved in establishing tensile strength and putatively intracellular transport guidance to axons and dendrites [154]. The authors conclude that preservation of the neuronal architecture may promote/facilitate nerve regeneration after nerve injury.

There have been several more studies investigating the role of stem cells in BCNI in rats, either alone [155] or in combination with PDE5 inhibitors [156, 157]. Furthermore, Lin et al. reported that adipose-derived stem cells (ADSCs) injected into the corpora cavernosa migrated within days to the bone marrow and then to the MPG [158]. Subsequent work has been reexamined in multiple systematic reviews and meta-analyses, reiterating the efficacy of these methods in 12 studies, n = 319 rats and 20 studies, n = 248 rats, respectively [159, 160]. The combination of stem cells + PDE5 inhibitor therapy appears to have the greatest effect [159]. Consistent outcomes among the studies were increase in the ICP/MAP ratio, levels of neuronal nitric oxide synthase, cavernous smooth muscle content, ratio of cavernous smooth muscle to collage, and cGMP levels [160]. Furthermore, stem cells modified by growth or neurotrophic factors

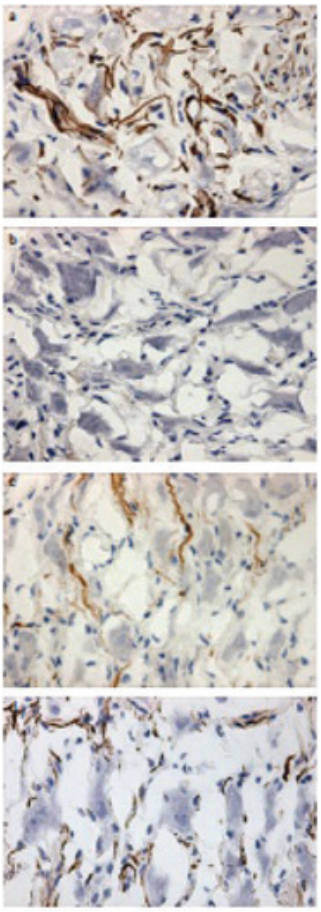

**Figure 12.** Neurofilament staining in major pelvic ganglion (MPG) of rats after bilateral cavernosal nerve crush injury (BNCI). A. Sham surgery. B. BCNI alone C. BCNI + neuronal stem cells injected into corpora cavernosa. Reprinted from Bochinski et al. [153].

prior to implantation appeared to exert the greatest benefit [160]. Although there are many processing steps to refine and standardize, this approach remains a riveting endeavor in the arena of penile rehabilitation.

## 7. Penile prosthesis implantation

Despite these advances in the restoration of endogenous erectile function after radical prostatectomy, some men will have dysfunction refractory to the above treatments. The final line treatment option for such patients is insertion of a penile prosthesis, which may in fact be conceived as a type of mechanotherapy. This procedure eliminates the possibility of any

spontaneous erectile function in the future and has many potential complications, including pain, erosion, extrusion, infection, mechanical failure, need for revision, and altered penile sensation. There have been a number of surgical improvements that have reduced the infection rate, including the "no touch" technique, standardized protocols for perioperative antibiotics, and the development of antibiotic-impregnated and hydrophilic devices [161–164]. Although the technique of 3-piece penile prosthesis insertion is beyond the scope of this chapter, there are a number of considerations with regard to radical prostatectomy. The cavernosal smooth muscle fibrosis and penile shortening can have an impact on the size of the cylinders able to be accommodated by the corpora, leading to actual or perceived reduction in penile length. Furthermore, the lack of glans tumescence with cylinder expansion may exacerbate the perceived loss of size. After appropriate dilation of the corporal bodies with the dilators, fibrosis should not preclude placement of a three-piece inflatable prosthesis, which has been reported to have the highest satisfaction rates and lowest rate of mechanical failure [165]. Some models of the 3-piece prosthesis (i.e. American Medical Systems, AMS 700 CX) allow for cylinder axial expansion to allow girth. This is important for men with penile plaques/Peyronie's disease and penile curvature that must be corrected during placement of the prosthesis [164]. Although not previously discussed, Peyronie's disease is another "sexual" complication of radical prostatectomy, thought to be from repetitive "buckling" injury to the phallus as a result of intercourse in the setting of an incomplete erection.

Reservoir placement during the three-piece prosthesis surgery also deserves consideration, given the previous dissection of the space of Retzius during the prostatectomy. Given the increased risk of bladder perforation, bowel and vascular injury in this setting, some authors favor ectopic reservoir placement just posterior to the rectus muscle and anterior to the transversalis fascia [166, 167]. Single-institution series have reported excellent outcomes with this approach [166, 167].

Satisfaction with this treatment appears favorable, as exemplified in a recent study of n = 71 patients who underwent penile prosthesis implantation after radical prostatectomy [168]. Pillay et al. employed the EDITS and SEAR questionnaires, as well as the Prostate Cancer-Related Quality of Life Scale and Patient Health Questionnaire-9 (PHQ-9) for both patients and their partners. They reported good sexual function (EPID score > 60) in 77% of men and treatment satisfaction in 94% (EDITS score > 50). Other studies have actually reported improved satisfaction for men undergoing early penile prosthesis insertion compared to those receiving sildenafil or intracavernosal injection therapy 6 months after radical prostatectomy [169, 170]. Such studies did not employ early aggressive pharmacologic penile rehabilitation programs, however. Certainly, for the appropriately selected patient, penile prosthesis implantation has a very high level of success and satisfaction for patients and their partners alike.

## 8. Conclusions

There have been many advances in the understanding of erectile dysfunction as a result of radical prostatectomy since the initial pioneering work by Walsh & Donker almost 40 years ago. Refined understanding of neuroanatomy, beneficial modifications in surgical technique,

the advent of robotic surgery, and the exploration of pre- and post-operative rehabilitation techniques using mechanotherapy and pharmaceuticals have improved the prognosis for potency recovery after this once morbid surgery. Further developments in the realm of local and systemic therapies for cavernous nerve neuroprotection and regeneration may mitigate the cascade of cavernosal smooth muscle apoptosis, fibrosis, and veno-occlusive dysfunction that jeopardizes further erectile function recovery after the period of post-operative neurapraxia. Achievement of the Trifecta is extremely important to patients and clinicians alike, and will surely inspire the future waves of investigations that continue to elucidate this field.

## Conflict of interest

I have no conflicts of interest to disclose.

## Notes/Thanks/Other declarations

None.

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